TE AHO O TE KAHU
CANCER CONTROL AGENCY

Mārama ana ki te Āputa: he tātari i te wāteatanga o ngā rongoā mate pukupuku i Aotearoa

Understanding the Gap: an analysis of the availability of cancer medicines in Aotearoa

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TE AHO O TE KAHU CANCER CONTROL AGENCY

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HE KUPU TAKAMUA
FOREWORD

Each year, 25,000 people are diagnosed with cancer in Aotearoa. The question of what treatment is available is a vital one for each of these patients, their whānau and the health professionals that look after them.

Cancer medicines – whether curative or life prolonging – are a critical part of cancer care. Better cancer outcomes are more likely to be achieved when there is equitable access to effective medicines. People living with cancer and their whānau often rely on cancer medicines and, understandably, expect that when they need a cancer medicine, it will be available.

As Te Aho o Te Kahu, the Cancer Control Agency, we are responsible for providing leadership and oversight of all aspects of cancer control in Aotearoa, from prevention to diagnosis, management and beyond. Increasingly, concerns have been raised about the availability of certain cancer medicines in Aotearoa compared with their availability in similar countries. These concerns have often been voiced by people living with cancer or their whānau, as they try to ensure they are getting the best possible treatment. It is these concerns that have motivated us to undertake this work and publish this report. We wanted to understand more about the gaps in cancer medicines funded in Aotearoa compared with Australia, to inform our work and the advice we give to Government.

The funding of cancer medicines is complicated. The rapid development of cancer drugs has created a challenge for governments to assess what added clinical benefit a new medicine may offer and how much money should be allocated towards a new medicine. The role of Pharmac is important, and not easy. We hope this report will be a useful additional resource for Pharmac in their work. At the time of publication, Pharmac is undergoing an independent review. We look forward to the outcome of that review and hope this analysis complements it.

In the next 20 years, it is expected that the number of people diagnosed each year with cancer will have increased by 40 percent. For that reason, it is important we balance the opportunities that effective cancer medicines offer, with other opportunities to improve cancer outcomes and reduce cancer inequities for Aotearoa. We must continue to help prevent as many cancers as possible while also providing high-quality diagnosis and treatment services for those who have cancer.

While this is a relatively detailed and technical analysis, in developing this report, we have aimed to keep people at the centre. I'd like to acknowledge the team that led this work and the national and international experts who provided their wisdom and insights to inform it.

We take seriously our responsibility at Te Aho o Te Kahu to serve the people of Aotearoa to ensure there are fewer cancers, better survival and equity for all. We hope this report will help to inform cancer policy decisions for Aotearoa going forward – and most importantly – benefit those living with cancer.

Mauri ora

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NGĀ MIHI
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We also are grateful to Pharmac and Medsafe staff for their input around specific aspects of this work.

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HE WHAKAMĀRAMA DEFINITIONS

Adjuvant: Additional treatment that is given after the primary treatment (for instance, cancer surgery) with the goal of destroying any remaining cancer cells.

ASCO: American Society of Clinical Oncology; an international professional organisation for medical oncology.

Available medicines: For the purposes of this report, this is defined as publicly funded medicines. For Aotearoa, this means medicines funded by Pharmac (see definition of 'Pharmac' below).

Best supportive care: Where no active treatment is given for the cancer, instead any treatment or interventions are focused on improving or maintaining quality of life. In some cases, this will also involve active monitoring for cancer progression. It may also include palliative treatment, such as palliative radiotherapy, with the aim of controlling symptoms.

Biosimilar: A highly similar, but not identical, version of an approved biologic medicine where there are no clinically meaningful differences between the reference biologic product and the biosimilar (Tabernero et al 2016).

Blood cancers: Cancers of blood cells. Also known as haematological cancers or haematological malignancies. Examples include leukaemias, lymphomas and multiple myeloma.

BRAF: B-Raf proto-oncogene serine/threonine kinase protein; a protein involved in cell growth and signalling. Mutations in the BRAF gene within cancer cells can cause abnormal cell growth and spread, which may play a role in some cancer types, including melanoma and colorectal cancer. Detecting BRAF mutations may help with planning treatment.

BRCA: Two breast cancer genes (BRCA1 and BRCA2) that produce proteins that help repair genetic material. Inherited (also called germline) mutations in the BRCA gene carry a higher risk of breast, ovarian, and several other cancers. Mutations can also occur just in the cancer cells (called somatic mutations). Detecting BRCA mutations may help with predicting and managing cancer risk, and with planning cancer treatment.

Chemoradiation: Treatment that combines chemotherapy with radiotherapy.

Chemotherapy: A type of cancer treatment that uses medicines to destroy or slow the growth of cancer cells. It may be given alone or with other cancer treatments, such as surgery or radiotherapy, and can be given in a variety of ways, including by mouth or infusion, depending on the type and stage of the cancer being treated.

Consolidation treatment: Treatment that is given together with or after the main treatment option, with the aim of deepening the response to treatment.

Curative intent treatment: Treatment given with the goal of achieving a complete remission and preventing the recurrence of cancer (Neugut and Prigerson 2017).

Disease-free survival: A surrogate (or proxy) endpoint often used in clinical trials of cancer medicines. Definitions may differ from study to study, but generally this term is used to mean the length of time that a patient lives without any signs or symptoms of the cancer after the main curative treatment for their cancer has ended. Disease-free survival results are often described using the median (see definition of 'Median' below). May also be known as relapse-free survival (see definition below).

EGFR: Epidermal growth factor receptor; a protein that is involved in cell growth and survival. Mutations in the EGFR gene within cancer cells can cause abnormal cell growth and spread, which may play a role in some cancer types, including non-small cell lung cancer. Detecting EGFR mutations may help with planning treatment.

EMA: European Medicines Agency; the agency responsible for the regulatory approval of medicines for European Union (EU) member states.

ESMO: European Society of Medical Oncology; an international professional organisation for medical oncology.

ESMO-MCBS: European Society of Medical Oncology – Magnitude of Clinical Benefit Scale; a tool used to assess the magnitude of benefit of medicines for solid tumours, based on information from clinical trials.

FDA: Food and Drug Administration; the agency responsible for the regulatory approval of medicines in the United States of America.

First-line therapy: The first treatment that is given in a particular treatment setting. For example, the first line of treatment in metastatic breast cancer may not be the first treatment the patient has received for breast cancer, but it is the first line of treatment they have received in the metastatic setting (see also definition of 'Line of treatment' below).

Germline: Inherited mutations that are present at birth, passed from parent to child.

HER-2: Human epidermal growth factor receptor 2; a protein involved in cell growth and survival. Mutations in the HER-2 gene within cancer cells can cause abnormal cell growth and spread, which may play a role in some cancer types, including breast, ovarian, bladder, pancreatic, and stomach cancers. Detecting HER-2 mutations may help with planning treatment.

Immunotherapy: A type of cancer treatment that uses medicines or other substances to activate a person's immune system to identify and target cancer cells. There are different types of immunotherapy, including checkpoint inhibitors and monoclonal antibodies (sometimes also called targeted therapy).

Incidence: The number of new cases of a disease, injury or medical condition in a population over a specified period of time.

Indication: The reason for using a particular medicine or treatment. For example, headache is one indication for paracetamol.

Line (of treatment): When talking about cancer medicines, the term 'line' or 'lines' of treatment is used to refer to what order different treatments are used in, or how many different treatments have been used to treat a person's cancer. For example, a first line of treatment for a person with cancer might be a course of chemotherapy; a second line of treatment for that person might then be a targeted treatment, used only if the cancer progresses after the first line of treatment has started.

Maintenance treatment: Treatment that is given together with or after the main treatment option, with the intent of lengthening the duration of or maintaining the response to treatment.

Median: The mid-point of a range. In clinical trials of cancer medicines, the median is often used to describe the point in time at which half the people in a study population reached a specified endpoint. For example, a median overall survival timepoint is the point in time when half the people receiving a given treatment are still alive.

Medicine-indication pair: A medicine linked to a specific indication. For example, paracetamol for headache would be one medicine-indication pair.

Medsafe: New Zealand Medicines and Medical Devices Safety Authority; the authority responsible for the regulatory approval of therapeutic products for use in Aotearoa, based on an assessment of the efficacy and safety of those products. Medsafe approval does not guarantee public funding.

Neoadjuvant: Treatment given to reduce the size or extent of the cancer before the main treatment, which is usually surgery, is given.

NHS: National Health Service; the national health service in the United Kingdom, consisting of four publicly funded healthcare systems (NHS England, NHS Scotland, NHS Wales and Health and Social Care in Northern Ireland).

NICE: National Institute for Health and Care Excellence; the agency in the United Kingdom that provides national guidance and advice to National Health Service (NHS) England and NHS Wales, including health technology assessments for new cancer medicines.

Non-curative intent treatment: Treatment that is given with the intent of prolonging life and/or improving quality of life but where a cure of the underlying cancer is unlikely to be achieved.

Overall survival: An outcome measure often used in clinical trials of cancer medicines. Definitions may differ from study to study, but in general, this is the length of time from allocation of treatment to death from any cause. Overall survival results are often described using the median (see definition of '**Median**' above).

PBAC: Pharmaceutical Benefits Advisory Committee; an independent statutory body in Australia responsible for recommending new medicines for funding via the PBS (see definition of '**PBS**' below).

PBS: Pharmaceutical Benefits Scheme; a scheme that provides universal access to funded medicines for people living in Australia (in broad terms, Australia's equivalent to Pharmac for Aotearoa).

Pharmac: Te Pātaka Whaioranga / Pharmaceutical Management Agency; the New Zealand Government organisation that is responsible for approving medicines for public funding in Aotearoa based on a number of factors, including unmet need, effectiveness, value for money, budget impact and suitability for use.

Prevalence: The number of people with a disease, injury or medical condition in a population at a given point in time.

Progression-free survival: A surrogate (or proxy) endpoint often used in clinical trials of cancer medicines. Definitions may differ from study to study, but in general, this is the time from allocation of treatment to either cancer progression or death from any cause. Progression-free survival results are often described using the median (see definition of '**Median**' above).

Quality of life: The degree to which a person feels healthy, comfortable and able to participate in or enjoy life events. This can mean different things to different people and can be heavily influenced by things such as a person's culture and value systems. In clinical trials of cancer medicines, changes in quality of life may be reported, using a variety of methods.

Radiotherapy: A type of cancer treatment that uses high-dose radiation to destroy or damage cancer cells. It can be used to cure cancer (curative radiotherapy), with other treatments to make treatment more effective (neoadjuvant or adjuvant radiotherapy), or to relieve symptoms (palliative radiotherapy). Also called radiation therapy.

RAS: Proteins that are involved in cell signalling. Mutations in the RAS genes (KRAS, HRAS and/or NRAS) within cancer cells can cause abnormal cell growth and spread, which may play a role in some cancer types, including colorectal and pancreatic cancers. Detecting RAS mutations may help with planning treatment.

Regimen-indication pair: Medicines that must be used in combination for a specific indication, for example, dabrafenib and trametinib used in combination for the treatment of unresectable melanoma would be one regimen-indication pair.

Regulatory agency: A government organisation responsible for approving a medicine for use, based on a balance of benefit and risk. For example, Medsafe is the regulatory agency in Aotearoa.

Relapse-free survival: A surrogate (or proxy) endpoint sometimes used in clinical trials of cancer medicines. Definitions may differ from study to study, but in general, this term is used to mean the length of time that a patient survives without any signs or symptoms of cancer, after the main curative treatment for their cancer has ended. May also be known as disease-free survival (see **definition above**).

Schedule: In medicines funding, a list of medicines that are available, under specific conditions and at specific prices. For example, in Aotearoa, the list of medicines available via public funding is Pharmac's Pharmaceutical Schedule. The comparable list in Australia is the PBS Schedule.

Second-line therapy: The second treatment that is given in a particular treatment setting, after the first-line treatment was shown to be ineffective or has stopped working. In some instances in this report, 'second-line therapy' is used to refer to second or subsequent lines of treatment. For example the second line of treatment in metastatic lung cancer would be used after the first (or prior) lines of treatment in that setting had either failed to work, or stopped working.

Solid tumours: Cancers that occur in cells or parts of the body outside of the blood system (ie, cancers that are not blood cancers). Examples include lung, breast, bowel and skin cancer.

Somatic: In genetics, somatic mutations are mutations that occur after conception and are not inheritable.

Surgical resection: A type of cancer treatment that involves surgically removing part or all of a tumour. It is often considered the definitive treatment for many solid tumours.

Targeted therapy/treatment: A type of cancer treatment that uses medicines or other substances to precisely identify and target certain types of cancer cells.

TGA: Therapeutic Goods Administration; the agency responsible for the regulatory approval of medicines in Australia.

WHO: World Health Organization; a specialised agency of the United Nations responsible for promoting health internationally.

Wild-type: A wild-type gene is a non-mutated or unaltered g

Mā te kimi ka kite,
mā te kite ka mōhio,
mā te mōhio ka mārama.

Seek and discover,
discover and know,
know and become
enlightened.

HE WHAKARĀPOPOTONGA
EXECUTIVE SUMMARY

What is this report about?

This report investigates the availability of medicines used in the treatment of cancer in Aotearoa New Zealand (Aotearoa). In this report, 'available medicines' means medicines that are publicly funded in Aotearoa via Pharmac. The report describes the findings of an analysis that compares the availability of cancer medicines here with that of Australia – not only in terms of the number of medicines funded, but also in terms of clinical benefit.

Why did we look into this topic?

Cancer medicines are a crucial part of the treatment of many different types of cancer – both solid tumours and blood cancers. Better cancer outcomes are more likely to be achieved when there is equitable access to effective medicines. People with cancer, and the people caring for them, rely on cancer medicines. They expect that when they need a cancer medicine, it will be available.

It is also important to recognise that the public funding of cancer medicines is a complicated issue. New medicines are being developed at a rapid pace. On the one hand, this provides much needed hope and options for people with cancer. On the other hand, the rapid pace of development and the high cost of cancer medicines can make it difficult for governments worldwide to assess what added clinical benefit new medicines offer and how much of finite public funds should be allocated towards new cancer medicines, relative to other needs that also require public funding.

In Aotearoa, Pharmac is the government agency responsible for deciding which medicines to fund across all areas of health, while the Government is responsible for deciding how much is allocated to medicines funding. Pharmac has a relatively unique approach to medicines funding compared with other countries. It is generally evident that there are fewer cancer medicines publicly funded in Aotearoa compared with other high-income countries with similar health systems, such as Australia. This difference in funding is a very real concern for people with cancer, their whānau, and the people and organisations caring for them.

Te Aho o Te Kahu is responsible for providing leadership and oversight of all aspects of cancer control in Aotearoa, from prevention through to diagnosis, management and beyond. In our work we often hear people's concerns regarding cancer medicines availability. The purpose of this analysis was to help us better understand the gaps in the availability of cancer medicines in Aotearoa, a particularly complex area of cancer care.

What did we do?

To understand the gaps in cancer medicines funding in Aotearoa, we compared the medicines that are currently publicly funded here with the medicines publicly funded in Australia. We looked at the number of medicines, as well as the specific cancers they are funded to treat. When identifying gaps, we linked together the medicine with the specific cancer type where it is used-we called these medicine-indication pairs. It was important to do this because certain medicines can be used to treat many different types of cancer, so just looking at the medicines alone would not tell the full story.

To assess the clinical benefit associated with any identified gaps in funding, we used an internationally recognised tool – the European Society of Medical Oncology – Magnitude of Clinical Benefit Scale (ESMO-MCBS). This scoring tool considers evidence from clinical trials of medicines for solid tumours, using measures such as survival and quality of life. Using this tool allowed us to distinguish between medicine-indication pairs that are likely to provide substantial additional clinical benefit over and above the medicines already funded in Aotearoa, and medicine-indication pairs that are likely to have less clinical benefit. Because the tool is only validated for medicines used to treat solid tumours (ie, not medicines for blood cancers), we have only been able to fully assess the situation for solid tumours at this time. We plan to conduct a similar analysis for medicines used to treat blood cancers, as soon as a similarly validated tool to assess clinical benefit becomes available.

The ESMO-MCBS is designed to inform policy decisions on cancer medicines, rather than specifically inform clinical decisions at an individual level. We acknowledge that what this tool defines as substantial clinical benefit may, in many cases, be different to what is considered meaningful to an individual patient and their whānau.

For those gaps with an ESMO-MCBS score indicating substantial clinical benefit, we sought expert clinical advice to confirm the relevance of the score to Aotearoa and describe how filling the gap would alter current clinical practice here.

What did we find?

We identified 20 different medicine-indication pair gaps, across nine different solid-tumour cancer types, where the medicines were publicly funded in Australia and not in Aotearoa, and where the ESMO-MCBS score indicated that the medicine would offer substantial clinical benefit. This does not mean that 20 different medicines would need to be funded to fill these gaps; the number of unique medicines was actually 18. This is because there was some overlap of the medicines that could be used, some medicines must be used in combination, and in some cases, there was more than one medicine to fill a gap.

Three of the 20 medicine-indication gaps were in the curative context, entailing five unique medicines. For these gaps, the medicines are used alongside surgery with the intent to cure, to reduce the possibility of the cancer from coming back after it has been removed. One of these gaps was for a medicine used in a specific type of breast cancer, and the other two were for two specific types of melanoma.

The remaining 17 medicine-indication gaps (entailing 17 unique medicines) were in the non-curative context. For these gaps, the medicines are being used with the intent of either extending a person's life, or improving the quality of their life, or both. In these treatment settings it is not expected that the cancer will be cured. These gaps were for medicines used across eight different cancer types: lung (five gaps), bowel (two gaps),

liver (one gap), kidney (three gaps), bladder (one gap), ovarian (two gaps), head and neck (one gap), and melanoma (two gaps).

For each of the 20 identified gaps, we described the clinical context and population-level epidemiology (such as how many people are diagnosed with the cancer, survival rates and existing inequities). We described what additional health service requirements might be needed if the gaps were funded, such as extra imaging. We also included what additional things patients might need to consider, such as more time receiving treatment or more blood tests. The gaps were all for targeted cancer medicines rather than for traditional chemotherapy. Some of these medicines are given by infusion and mean extra health care resources are needed and patients may have additional travel requirements. Others are tablets and could free up health care resources. Some have specific side-effects that are quite different to traditional chemotherapy and require specialised management.

We also looked at whether these gaps were currently within Pharmac's processes for assessment, and, if so, where in that process they were. Many of the gaps are either under active assessment, or have already been assessed for funding by Pharmac and are now 'Options for Investment' – that is, awaiting available funds to be made available in Aotearoa. Since the time of our analysis, two of the identified medicines have been approved for funding by Pharmac: durvalumab for a certain type of lung cancer, and olaparib for a certain type of ovarian cancer.

Additional gaps were identified for medicines used in the treatment of blood cancers. These were not assessed for clinical benefit due to the absence of a validated assessment tool.

What happens next?

The analysis presented in the report is our first step in better understanding this important issue of gaps in cancer medicines funding. The detailed gap analysis was necessarily limited to solid tumours, and we plan to conduct a similar analysis for medicines used to treat blood cancers once a validated tool – like the ESMO-MCBS – is available to assess clinical benefit in blood cancers.

By identifying and describing gaps in cancer medicines for solid tumours, together with the relevant context, we hope to provide useful insights to Pharmac, the New Zealand Government, the health sector and to the public. This analysis was conducted separately to the independent review of Pharmac announced by the Government in March 2021, but preliminary results of this analysis were shared with the Pharmac Review Panel.

The findings of this analysis are important to help optimise the role that cancer medicines play in improving cancer control in Aotearoa. Cancer medicines are an integral part of cancer care. However, cancer medicines do not and should not exist in isolation. The full benefits of cancer medicines can only be realised if the whole spectrum of cancer care – from early detection through to diagnosis, staging, treatment, follow-up and supportive care – is working well and equitably, and if there is adequate workforce to deliver all aspects of cancer care, including medicines. Strengthening the cancer continuum as a whole remains the key objective for Te Aho o Te Kahu, and is essential to deliver on the goals of fewer cancers, better survival, and equity for all.

KŌRERO O MUA
BACKGROUND – The opportunities and challenges of cancer medicines

Cancer medicines are critical to high-quality cancer care

Cancer is the second leading cause of mortality globally and the leading cause of death and health loss in Aotearoa New Zealand (Aotearoa) (Te Aho o Te Kahu 2021a). Each year in Aotearoa, approximately 25,000 people are diagnosed with cancer and 9,000 people die from cancer (Ministry of Health 2020). The burden of cancer and its disproportionate impact on Māori, Pacific peoples and other priority population groups have been described in detail in *He Pūrongo Mate Pukupuku o Aotearoa 2020, The State of Cancer in New Zealand 2020* (Te Aho o Te Kahu 2021a). These inequities are avoidable and unfair and are a result of many factors, including differential exposure to cancer risk factors and poorer access to screening programmes and health services. (Hill et al 2010, McLeod et al 2010, Robson et al 2010, Seneviratne et al 2014, Tin Tin et al 2018). Access to cancer medicines can also contribute to disparities in outcomes.

Better cancer outcomes are much more likely when there is timely diagnosis and access to the right treatment. Cancer medicines are one of several key treatment modalities, alongside interventions such as surgery, radiotherapy and bone marrow or stem cell transplantation. While surgery and radiotherapy are generally the definitive treatments for many solid tumours, as are bone marrow or stem cell transplants for some blood (haematological) cancers, cancer medicines have a critical place in cancer care. Cancer medicines are administered with the goal of achieving complete remission of the cancer and preventing recurrence (curative intent treatment), or slowing the progression of cancer or relieving symptoms and improving quality of life (non-curative intent treatment). For an individual impacted by cancer and their whānau, the hope of even a small improvement in quantity or quality of life can be incredibly important.

Availability and accessibility of cancer medicines is a challenge in Aotearoa and internationally

Access to appropriate and effective cancer medicines is central to high-quality cancer care. Worldwide, patients and their clinicians have expectations of timely access to new cancer medicines that have been shown to be effective, and these expectations are increasingly not being met. It is well established that there are fewer cancer medicines available in Aotearoa compared with other high-income countries, such as Australia (Wonder and Fisher 2016, Evans et al 2016, Wonder and Milne 2011), the United Kingdom (UK), the United States of America (USA) and Canada (Cheema et al 2012). Worldwide, the availability and funding of new and effective cancer medicines are often well publicised and unsurprisingly emotive issues for patients and their whānau, clinicians, and advocacy groups. There are many reasons why the funding of cancer medicines is challenging, and these are outlined in more detail below.

New cancer medicines are being developed at a rapid pace

As cancer incidence increases globally, in part due to population growth and people living longer, more people need cancer treatment. Greater understanding of the molecular basis of cancer has led to the rapid development of new medicines, including targeted medicines and immunotherapy, which have resulted in more effective treatments and improvements in patient care. Treatment for many cancers is continuously evolving, with more indications for treatment, greater use of precision-driven medicine, and increasing lines of therapy available to patients. This has resulted in an increased use of combination therapies, extended treatment regimens and additional lines of therapy. A significant challenge in this rapidly evolving environment is that there can often be uncertainty surrounding the degree of clinical benefit offered by a new medicine.

Spending on cancer medicines is increasing

Increasing cancer incidence and the growing use of more cancer medicines by more patients have all contributed to an exponential increase in the overall use of cancer medicines globally. At the same time, cancer medicines are significantly more expensive than medicines for most other diseases, and their prices are rising more quickly than medicines for other conditions (Bach 2009, Savage et al 2017). There is concern that the costs of cancer medicines do not correlate with value or clinical benefit (Jiang et al 2019, Vivot et al 2017, Vokinger et al 2020). For instance, between the 1990s and early 2000s, cancer therapies for metastatic colorectal cancer improved outcomes for patients by nearly doubling the median survival time but with a 340-fold increase in cost (Schrag 2004).

Pharmaceutical companies argue that the high pricing of cancer medicines is because of high development costs – and for rare diseases, an extra consideration is the comparatively small patient population (WHO 2018). In 2019, cancer medicines sales generated a significant proportion (around one-quarter) of the total drug revenue among 10 large pharmaceutical companies (Meyers et al 2022). The same study showed that revenue from the sale of cancer medicines increased by 70 percent over the last decade, while revenue from the sale of other medicines decreased by 18 percent.

New cancer medicines are costly and increasingly unaffordable for health care systems and patients around the world. Several high-income countries, including Aotearoa and Australia, spent around 10 to 20 percent of total pharmaceutical expenditure on cancer medicines in 2019 (Hofmarcher et al 2021). With finite resources available for health care, health systems are continually faced with deciding how to balance investment in cancer medicines against other priorities, and there is no correct answer to the issue of how much is the right amount to spend on cancer medicines. In countries with publicly funded health care, the rising cost of cancer medicines impacts the sustainability of such systems. In other countries, these costs are passed onto cancer patients, who can encounter catastrophic personal financial hardship when accessing cancer care (Fundytus et al 2021).

It can be difficult to assess the added clinical benefit of new cancer medicines

Most new cancer medicines are approved and marketed based on clinical trial data showing statistically significant improvements in end points such as improvements in length of life (often called 'overall survival'), or surrogate measures such as time to disease progression or recurrence (often called 'progression-free survival' or 'disease-free survival'), when compared with a placebo or another established treatment.
A surrogate measure is one that is intended to indicate that a clinical end point will be achieved in the future, but surrogate measures do not always correlate well with clinical outcomes. Accelerated approval pathways based on surrogate outcomes are increasingly and commonly being used by pharmaceutical regulatory bodies, including the United States' Food and Drug Administration (FDA) and the European Medicines Agency (EMA), to facilitate and expedite the development and review of new cancer medicines (Gyawali et al 2022, Molto et al 2020, Wang et al 2021).

Some cancer medicines will have large and indisputable benefits (such as improved overall survival of months or even years), while other medicines may offer only marginal improvements (such as progression-free survival improvements of a few weeks or less without any accompanying overall survival or quality-of-life benefit). Furthermore, many cancer medicines are marketed without strong evidence of an improvement in patient-centred outcomes, such as quality of life (Prasad 2017).

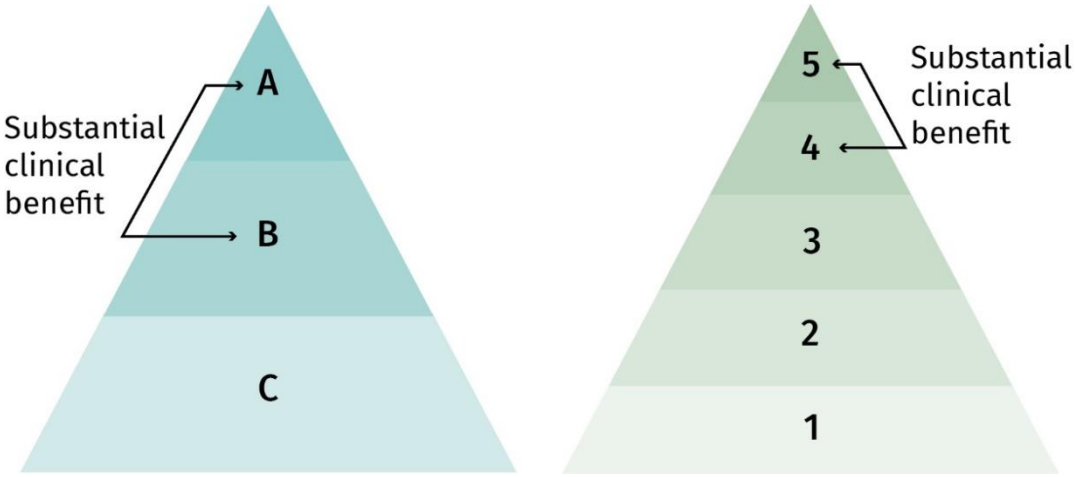
There are some tools to help assess the added clinical benefit of cancer medicines

Given the challenges described above, various organisations and clinical societies have developed tools to help evaluate the clinical benefit of new cancer therapies. These tools are intended to assist health systems, clinicians and patients in their decision-making around the use of cancer medicines.

The two most widely used tools are the European Society of Medical Oncology – Magnitude of Clinical Benefit Scale (ESMO-MCBS) and the American Society of Clinical Oncology's (ASCO) Value Framework. Both these tools have been developed to assess the clinical benefit of medicines for solid tumours. While the ASCO Value Framework is intended to help individual patients choose a medicine in shared decision-making with their oncologist (Vokinger et al 2020), the ESMO-MCBS assesses the magnitude of clinical benefit of cancer medicines to inform decisions about cancer medicines at a policy and population level (ESMO nd-a). The highest grades of the ESMO-MCBS, indicating a substantial clinical benefit, are a score of A or B in a curative setting and 4 or 5 in a non-curative setting (Figure 1). What is required for a cancer medicine to score A, B, 4 or 5 varies depending on the scenario, but measures such as overall survival, disease-free survival, progression-free survival, quality of life, toxicities and, in some cases, cost savings are considered. For example, in the curative setting, an ESMO-MCBS score of A or B represents a minimum of a 3 percent increase in the number of people alive after three years (ie, an improvement in overall survival) or improved quality of life – even in the absence of a survival benefit. In the non-curative setting, the definitions vary further based on the prognosis of the condition.

A recent comparative assessment of the ESMO-MCBS and ASCO Value Framework reported moderate concordance between their clinical benefit scores in the non-curative setting (Cherny et al 2018). It should be noted that many cancer medicines that are approved by the FDA for advanced solid tumours do not meet the ESMO-MCBS or ASCO-Value Framework threshold of substantial clinical benefit (Jiang et al 2019, Vivot et al 2017). Similarly, some cancer medicines studies report gains in either progression-free survival and/or overall survival as 'meaningful' that do not meet either the ESMO-MCBS or ASCO Value Framework thresholds for substantial clinical benefit (Dreicer et al 2017).

Figure 1: Categories according to the ESMO-MCBS in the curative (left) and non-curative (right) settings



Source: ESMO 2021

There is no equivalent value assessment framework or tool that has been developed or validated for blood cancers. In 2020, a collaborative study was published by the European Haematology Association (EHA) and ESMO (Kiesewetter et al 2020). This was a feasibility assessment to determine whether the ESMO-MCBS could be applied to clinical trials for medicines in blood cancers, using a subset of blood cancer types. While the authors found that in many cases the tool could be applied, they also found that the tool was either unable to be applied or inappropriate to apply to some of the studies. The authors noted that this was because of important differences between solid tumours and blood cancers. Based on the findings of this study, ESMO and EHA have committed to develop a version of the score that is robustly validated to grade medicines for blood cancers.

Another tool used internationally to assess the relative value (based on clinical benefit) of medicines is the World Health Organization's Essential Medicines List (WHO-EML).[1] The World Health Organization includes cancer medicines on its model Essential Medicines List (EML) – for both solid tumours and blood cancers – to support decision-making at a policy or programme level, especially in low-resource settings. The intent is to distinguish medicines that should be prioritised for national listing and procurement from those that provide marginal or no benefit (WHO 2020). The EML specifically considers the magnitude of clinical benefit associated with treatment (WHO 2020), and ESMO–MCBS has been used to screen for cancer treatments that warrant consideration for the EML since 2019 (WHO 2020).

[1] There are separate adult and child model EMLs (for further information, see www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines/essential-medicines-lists).

Countries make decisions about the value of cancer medicines differently

Head-to-head comparisons of the availability of cancer medicines across different countries must be made cautiously, as there are large and important differences in how cancer medicines are approved, assessed, funded and implemented across countries. Each of these factors influences not just how many and which cancer medicines are made available but also how comprehensive and consistent access is.

The approach to medicines funding in Aotearoa

In Aotearoa (and internationally), a medicine cannot be made generally available to patients until regulatory approval has been granted. Medicines are approved by regulators when the likely benefit of treatment outweighs the likely risk of harm. Unlike most other countries, once a medicine has regulatory approval in Aotearoa, it can be advertised directly to patients. In Aotearoa, Medsafe (New Zealand Medicines and Medical Devices Safety Authority) is the regulatory authority (see **Table 1**). Medsafe may complete its own entire risk-benefit assessment for regulatory approval or base its assessments on those of other international regulators (such as the FDA or Australia's TGA). Medsafe is not responsible for assessing medicines for funding. In Aotearoa, this responsibility is held by the governmental agency Te Pātaka Whaioranga | Pharmaceutical Management Agency (Pharmac), which assesses and makes decisions about medicine funding and manages the budget for medicines funding. Usually, Pharmac's assessment occurs after Medsafe approval.[2] Pharmac has a special parallel assessment path for cancer medicines (and medicines for rare diseases). Cancer medicines can be considered for funding by Pharmac at the same time as they are undergoing Medsafe's regulatory assessment, rather than after Medsafe approval (Pharmac 2020a).

Pharmaceutical companies, clinicians and consumers can apply to Pharmac for a medicine to be publicly funded. Pharmac's external clinical advisory groups provide advice to Pharmac on the funding applications it receives, using a framework that considers need, health benefits, costs and savings, and suitability (Pharmac 2020b). Funding applications are then assessed further by Pharmac and are categorised into three lists: Options for Investment (those that would be funded if budget allowed), Only if Cost Neutral or Cost Saving (those that would be funded if a cost neutral or cost saving deal could be negotiated, generally on the basis that they offer no substantial health benefit over what is currently funded) and Recommended for Decline (those that would not be funded, even if budget allowed, unless new information came to light) (Pharmac 2021b). The Options for Investment list is ranked in order of priority for funding, and this order is kept confidential to Pharmac. This confidentiality is to protect Pharmac's negotiating position (Pharmac 2021a). The applications' progress is published on Pharmac's Application Tracker, including which of the three lists each funding application has been assigned to.

[2] Further detail about how Pharmac assesses medicine applications for funding is available from the webpage at: **https://pharmac.govt.nz/medicine-funding-and-supply/the-funding-process/.**

Once a medicine has been ranked as an option for investment, Pharmac is responsible for procuring the medicine on behalf of district health boards (DHBs), using the available budget. Because it negotiates for contracts on a national scale, Pharmac's purchasing power means that it can achieve good prices on behalf of Aotearoa – rather than 20 different DHBs trying to negotiate with each pharmaceutical supplier.

Not all medicines that are ranked on the Options for Investment list are actually funded. This is because Pharmac operates within a fixed budget, set by the Government (NZ$1.085 billion for 2021/22 (Ministry of Health 2021). Pharmac is required by law to stay within its allocated budget for pharmaceuticals (New Zealand Parliamentary Counsel Office nd, Pharmac 2022a). This fixed budget is managed on behalf of DHBs and ensures that pharmaceutical spending does not exceed the country's ability to pay. Based on gross expenditure estimates, roughly 15 percent of the pharmaceutical budget is spent on cancer medicines.[3] However, it is not sufficient to pay for all new medicines that are deemed fundable. Current at 12 April 2022, there were 121 different applications listed as 'Options for Investment', and of these, 49 were for cancer treatments.

Medicines that have been approved for funding by Pharmac are listed on the national Pharmaceutical Schedule. These medicines are then available to all eligible patients who meet any related funding criteria, across public hospital inpatient and outpatient, and community settings. Patients eligible for publicly funded health and disability services do not have to pay for medicines administered in the hospital or in an outpatient setting at the hospital (Jatrana et al 2011). However, they generally have to pay NZ$5 for subsidised medicines on prescription from any pharmacy, or NZ$15 if it is a specialist prescription from a private specialist. Patients and their whānau who have collected 20 prescription items (NZ$100) in a year do not have to pay for any new prescriptions until the following year under the prescription subsidy scheme (New Zealand Government 2021). There are key differences in how medicines are funded in Aotearoa compared to other countries, as outlined below.

[3] This is a rough estimate based on gross (ie, before any rebates or other adjustments) expenditure for medicines used in cancer in the 2019/20 financial year (NZ$237.5 million) and total gross expenditure on medicines in that same year (NZ$1,646.9 million), using figures provided by Pharmac and published in its annual report. This estimate may not accurately reflect the proportion of net expenditure. Some medicines are used for cancer and for non-cancer medicines and this can complicate the calculations. Rituximab – which is a high cost medicine that is used for cancer and non-cancer indications was excluded. It is possible that other medicines used for cancer were inadvertently excluded and cancer medicines being used for non-cancer indications were included. Medicines funded via the paediatric cancer treatments pathway were excluded.

There is international variation in the value assessment, funding and procurement of cancer medicines

In Aotearoa, a single agency (Pharmac) assesses medicines for funding, decides which medicines are to be funded, and then funds and procures them. This is different to other countries that Aotearoa is often compared against (such as Australia, Canada, the UK and USA), where multiple separate entities look after each of these functions. In fact, Pharmac is the only government agency in the world that takes this approach (Pharmac, 2022c).

For example, in Australia, the Pharmaceutical Benefits Advisory Committee (PBAC) assesses submissions and recommends which medicines should be publicly funded. The Australian Government reviews PBAC recommendations and decides which medicines should be included on the government-subsidised Pharmaceutical Benefits Scheme (PBS). Similarly, in Canada, the pan-Canadian Oncology Drug Review (pCODR) assesses new cancer medicines and then makes funding recommendations to each Canadian province or territory (except Quebec).[4] Each jurisdiction makes its own decisions about which medicines to fund.

In the UK, England, Wales, Scotland and Northern Ireland have individual assessment and funding arrangements. For instance, the National Institute for Health and Care Excellence (NICE) makes the value assessments and delivers recommendations on which medicines should be funded by the National Health Service (NHS) in England (and usually Northern Ireland and generally Wales[5] also). It is then up to individual NHS clinical commissioning groups to arrange funding of the medicines. The USA has a complicated health care system comprising private insurers and public health coverage. Individual funders (eg, insurance companies and state governments) negotiate with pharmaceutical companies on the best price at which to fund medicines for individual patients. The exception is the national Medicare health insurance programme, which is legally required to pay for any medicine approved by the FDA without negotiation on price (Kantarjian and Rajkumar 2015).

Pharmac's fixed pharmaceutical budget is a key distinction of medicine funding in Aotearoa compared with these other countries – new medicines can only be funded using the savings achieved from medicines that are already funded, or if the Government approves an increase to the fixed budget. For example, in Australia, the PBAC considers each new medicine on its own merit, and the PBS budget can expand to accommodate new medicines. This results in access to more new medicines in Australia (compared with Aotearoa), along with an expanding pharmaceutical budget (Babar et al 2019). Similarly, the UK does not have a capped medicines budget, however, various policies aim to control pharmaceutical spending, including a robust cost-effectiveness assessment by NICE before it recommends a medicine for use, and contractual agreements between the NHS and pharmaceutical companies (Rodwin 2021).

[4] The Institut national d'excellence en santé et en services sociaux (INESSS) performs the health technology reviews for Quebec.

[5] The All Wales Medicines Strategy group advises NHS Wales. This group generally follows NICE decisions but can also issue its own guidance.

There is international variation in coverage, co-payments and out-of-pocket costs

In general, there is greater universal availability of medicines in Aotearoa once listed in the Pharmaceutical Schedule, with no inter-jurisdiction differences or differences by cancer treatment settings. Out-of-pocket costs – that is, the amount that an individual person has to pay towards their treatment – are also significantly lower in Aotearoa compared with other countries.

For example, in Australia, a medicine funded via the PBS is available to anyone who meets the funding criteria in the community and hospital outpatient setting but not in the inpatient setting, where individual hospitals or hospital networks decide which medicines are funded for inpatient use. Intravenous chemotherapy is free for inpatients at public hospitals, but in some states or territories, there may be out-of-pocket costs for cancer treatments administered in outpatient infusion clinics. Most outpatient prescription medicines are subsided via the PBS, and patients may expect to pay up to NZ$45. Although the cost of many cancer medicines is subsidised for those with a current Medicare[6] card, out-of-pocket costs can still be substantial for patients (Gordon et al 2018). These differences may have important implications for equitable access to medicines.

In Canada, medicines prescribed outside the hospital are not covered by the universal health insurance system. There is no national standard for prescription medicine coverage, and patients can access medicines either through government-funded plans or private health insurance coverage or they pay directly out of their own pocket. Each province offers its own government-funded programme that can cover medicines for eligible individuals, based on age, income and/or medical condition. However, some may have to pay the full cost of prescription medicines, and even those with insurance may still need to bear some or all the costs of their medicines.

There are differences across the UK in cost-sharing arrangements with patients for prescription drugs, apart from medicines prescribed in NHS hospitals that are free of charge. In Scotland, Wales and Northern Ireland, there is no charge for outpatient prescriptions. In England, people who are receiving treatment for cancer are eligible for free NHS prescriptions with a medical exemption certificate for five years.

In the USA, approximately 10 percent of the population (31.1 million people) were uninsured in 2021 (Cohen et al 2021), and many with insurance still incur high co-payments and out-of-pocket payments for medicines. High out-of-pocket costs for medicines presents a major concern for many people with cancer, and vary greatly depending on insurance and type of treatment received. The results can be financially catastrophic for some cancer patients in the US, even for basic treatments.

[6] Medicare is the publicly funded universal health care insurance scheme in Australia, operated by the social security section of the Department of Social Services, Australian Government.

Although there is greater availability of cancer medicines in Aotearoa once funded, and lower out-of-pocket costs, this does not necessarily guarantee accessibility, especially for Māori and Pacific peoples (Goodyear-Smith and Ashton 2019). For example, if a funded medicine needs to be given by infusion in a specialised infusion centre, but the person who needs it lives far away and does not have access to transport or accommodation, then the medicine is available, but not accessible.

Table 1: Summary of entities responsible for the regulation, value assessment, funding and procurement of new medicines, by country

Country	Medicines regulator	Medicines value assessment and recommendation for funding	National medicines procurement and contracting
Aotearoa	Medsafe	Pharmac	Yes – Pharmac
Australia	Therapeutic Goods Administration (TGA)	Pharmaceutical Benefits Advisory Committee (PBAC)	Yes – Australian Government / Department of Health
Canada	Health Canada	pan-Canadian Oncology Drug Review (pCODR) (all provinces/territories except Quebec) Institut national d'excellence en santé et en services sociaux (INESSS) for Quebec	No single entity – various public and private funders
United Kingdom	Medicines and Healthcare Products Regulatory Agency (MHRA) (also previously European Medicines Agency)	National Institute for Health Care and Excellence (NICE)	No – various NHS commissioners, including NHS England clinical commissioning groups
United States of America	Food and Drug Administration (FDA)	Various	No single entity – various public and private funders

What this analysis sets out to achieve

Given the opportunities and the challenges posed by cancer medicines described above, we wanted to better understand the current situation for cancer medicines availability in Aotearoa. We therefore conducted a descriptive analysis to compare cancer medicines availability between Aotearoa and one similar country (Australia) – considering not only the difference in number of medicines available, but also (where possible) the magnitude of clinical benefit associated with any gaps. Acknowledging the key differences in medicines funding across jurisdictions, we wanted to establish a system-level understanding of the current situation in Aotearoa, to inform future policy discussions.

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METHODS

Overview of the analysis

The main purpose of this analysis was to compare the availability of cancer medicines in Aotearoa with their availability in Australia, and to highlight gaps in availability that were likely to be associated with substantial clinical benefit. For the purpose of this analysis, a medicine was considered to be available if it was publicly funded.

As an initial check, a comparison was made with the WHO's Essential Medicines List to determine if cancer medicines considered essential by the WHO are being publicly funded in Aotearoa.

For the main gap analysis, Australia was selected as the primary comparator country, due to its broadly similar health system and approach to pharmaceutical funding, and the accessibility of detailed information regarding its cancer medicine funding. Gaps in cancer medicines' availability identified in both Aotearoa and Australia were assessed for clinical relevance and associated magnitude of clinical benefit according to the ESMO-MCBS scoring tool. This scoring tool was selected not only because it is internationally recognised and validated, but also because it is specifically intended for use in policy settings, given the purpose of this analysis was to consider medicines' availability at a systems level. Unfortunately, it has not been validated for medicines for blood cancers.

As there is no 'gold-standard' approach to the funding of cancer medicines, clinically relevant gaps for solid tumour medicines in Aotearoa associated with a substantial magnitude of clinical benefit were also compared with another funding jurisdiction – Ontario, Canada. This comparison was made as a test of whether Australia should be considered an outlier amongst other similar countries/jurisdictions. Again, Ontario was selected as it has a broadly similar health system, with funding of pharmaceuticals decided at the province level.

Medicine-indication pairs

Central to this analysis is the concept of medicine-indication pairs (or in some cases regimen-indication pairs). Indication is a medical term used to describe the reason for using a particular medicine or treatment. For example, headache is an indication for paracetamol. In this report, a medicine-indication pair is defined as a medicine that is linked to a specific cancer indication. The same applies to a regimen-indication pair, where more than one medicine must be used in combination (ie, as a regimen) for a given cancer indication. The use of medicine-indication pairs was necessary as cancer medicines funding is often restricted to specific indications – particularly for newer, higher cost medicines. This means that even if a certain medicine is funded in a given jurisdiction, it is not necessarily funded for every cancer type that it might be indicated for.

Scope and definitions of cancer medicines

For this analysis, cancer medicines were defined as medicines used to actively treat cancer. Medicines used exclusively to manage symptoms or side effects without any direct effect on the tumour, whilst critical to cancer care, were outside the scope of this analysis. Medicines for blood cancers were included when summarising the numbers of medicines and medicine-indication pairs available in different jurisdictions. However, when analysing gaps for magnitude of clinical benefit, blood cancer medicines were considered out of scope due to the absence of a validated tool to conduct this assessment. The ESMO-MCBS scoring tool has not yet been validated for blood cancers, and no other appropriate tool was found.

Where a generic or biosimilar product was available in one jurisdiction and the reference product (also called originator, innovator or brand-name product) was available in another, these were considered to be identical for the purposes of this analysis.

Scope and definitions of available cancer medicines

The scope of available cancer medicines in Aotearoa was limited to those funded via Pharmac's Pharmaceutical Schedule. Medicines publicly funded in Aotearoa via other means (eg, Pharmac's exceptional circumstances processes, paediatric cancer medicines or clinical trials in the public health setting) were excluded from the analysis. Medicines funded outside the public system (eg, via private financing, private health insurance or compassionate supply by pharmaceutical companies) were also excluded from this analysis.

The scope of available cancer medicines in Australia was limited to those included in the PBS schedule (Australian Government Department of Health 2022). This analysis focused on medicines that were consistently available across all of Australia. In line with that reasoning, the analysis excluded medicines publicly funded in Australia via other means, such as medicines used in the public hospital inpatient setting or where the funding is provided by an individual hospital or state government. Medicines funded via private means were also excluded from the analysis.

The scope of available cancer medicines in Ontario, Canada, was limited to those funded via one of the multiple public funding mechanisms available in that province, for example the New Drug Funding Program (NDFP) and the Ontario Drug Benefit (ODB) Program. Medicines funded via private means were again excluded from the analysis.

Definition of substantial clinical benefit

The thresholds for substantial clinical benefit were a score of A or B in a curative setting and 4 or 5 in a non-curative setting. These thresholds are in accordance with ESMO guidance (ESMO nd-b) (see Figure 1), and have been determined and validated previously using robust statistical methods (Cherny et al 2017, Cherny et al 2015, Dafni et al 2017). There is international precedent in applying the scores (WHO 2019a). As described above, these thresholds were only applied to medicines for solid tumours, as the ESMO-MCBS has not been validated for blood cancers.

In general terms, in the curative setting, an ESMO-MCBS score of A or B represents a minimum of a 3 percent increase in the number of people alive after three years (ie, an improvement in overall survival) or improved quality of life – even in the absence of a survival benefit. In the non-curative setting, the definitions vary further, depending on the prognosis of the condition. An ESMO-MCBS score of 4 or 5 can be based on overall survival improvements of a minimum of two months (only where there is an associated quality of life benefit proven), to over nine months. In the absence of overall survival benefit in the non-curative setting, an ESMO-MCBS score of 4 or 5 can be based on a progression-free survival improvement of 1.5 months (again, only with proven quality of life benefits) to over three months. Again, a medicine can score 4 based on improved quality of life even in the absence of a benefit in progression-free or overall survival. Medicines that have not met these clinical benefit thresholds in clinical trials will be scored C, 3, 2 or 1. A detailed description of the ESMO-MCBS scoring methods is available on the Guidelines page on the ESMO website at: www.esmo.org/guidelines/esmo-mcbs.

Information sources

All information regarding funding status was obtained from publicly available information. More specific detail regarding the information sources is provided in Appendix 1: Key sources of information.

Timeframe

Comparisons were made between the cancer medicines funded in Aotearoa and those on the WHO-EML and the Australian PBS using information available at 1 July 2021. The comparison with cancer medicines funded in Ontario, Canada, was made in October 2021.

There has been an updated EML since the time of analysis and, given the rapid pace of change in cancer medicines, it is likely that there will have been changes to cancer medicines funded in Australia and Ontario over this time as well. Any updates or additions to the EML, or changes in cancer medicines funded in Australia or Ontario were not captured by this analysis. However, where there were changes to the Pharmac Pharmaceutical Schedule subsequent to the analysis, this has been noted in the results.

Comparison with the World Health Organization's Essential Medicines List

Cancer medicines publicly funded in Aotearoa were compared with those included in the 21st WHO EML (WHO 2019b). All medicines included in section 8 ('immunomodulators and antineoplastics') of the EML were extracted. Medicines used for reasons other than the active treatment of cancer, such as supportive care medicines, were excluded. For each remaining medicine (and specific cancer indication where this was stated), a manual search of Pharmac's online Pharmaceutical Schedule was conducted. A manual search of Pharmac's application tracker was conducted for all medicines or medicine-indication pairs that were identified as not included in the Pharmaceutical Schedule. Any perceived omissions at the end of this process were individually assessed to determine if there were alternatives in the Pharmaceutical Schedule generally accepted as being equivalent, before being formally identified as a gap.

Comparison with Australia's Pharmaceutical Benefits Scheme

Cancer medicines publicly funded in Aotearoa were compared with those included in the Australian PBS schedule of pharmaceuticals using the stepwise process described below.

Collation of medicines available in Australia

All medicines included in section L of the PBS schedule ('antineoplastic and immunomodulating agents') were manually extracted from the PBS website (Australian Government Department of Health nd). For each medicine, the following information was considered: medicine name, formulation(s), relevant restrictions on funding where applicable (such as cancer type, cancer subtype, line of therapy and medicines required in combination). Medicines and indications were handled in the following ways:

- Where a medicine was listed for multiple different indications, each medicine-indication pair was considered separately.
- Different specified lines of treatment were considered to be different indications.
- Where multiple medicines were required to be used in combination for a given indication, these were considered together as a single regimen-indication pair.
- For medicines listed without restriction in Australia that were either not included or listed with restrictions in Pharmac's Pharmaceutical Schedule, specific indications were sought using the Australian TGA-approved product information (the equivalent of the Medsafe approved Data Sheet in Aotearoa) and eviQ[7] treatment protocols (Cancer Institute NSW nd-a). Each indication was then included as a separate medicine-indication (or regimen-indication) pair.

[7] eviQ is an online resource of cancer treatment protocols developed by multidisciplinary teams of cancer specialists for the Australian Government. eviQ provides evidence-based information used routinely by Australian health professionals in the delivery of cancer treatments.

Identification of gaps between Australia and Aotearoa

For each medicine-indication pair derived from the PBS schedule at the end of this process, a manual search of Pharmac's online Pharmaceutical Schedule was conducted. Additionally, a reverse comparison was also made – where the oncology and immunosuppressants section of the Pharmaceutical Schedule was assessed for medicines that were funded in Aotearoa but not included in the PBS schedule.

Assessment and categorisation of gaps for solid tumours based on ESMO-MCBS score

For medicine-indication pairs that were funded in both countries, no further analysis was undertaken and they were categorised as 'not a gap'.

An ESMO-MCBS score was obtained (if available) for medicine-indication pairs funded in Australia but not included in Pharmac's Pharmaceutical Schedule. Where there were multiple ESMO-MCBS scores available for the same or similar medicine-indication pair gap, the highest score was used. Where the PBS indication was broad and therefore covered multiple ESMO-MCBS scores, the highest score was used.

For medicine-indication pair gaps with an ESMO-MCBS score of 1 or 2, no further analysis was undertaken, and the gap was categorised as 'not substantial clinical benefit'. For gaps with an ESMO-MCBS score of 3 or C, an additional check of Pharmac's Pharmaceutical Schedule was made to see whether the comparator was funded. If the comparator was funded (or the comparator was a placebo) or there was no comparator (ie, a single-arm study), no further analysis was undertaken, and the gap was categorised as 'not substantial clinical benefit'.

For medicine-indication pair gaps for which there was no ESMO-MCBS score available or where the available ESMO-MCBS score was 3 or C but the comparator was not funded in Aotearoa, external clinical advice was sought. In the case of gaps with a score of 3 or C, the purpose of this advice was to determine whether the established ESMO-MCBS score should be upgraded. Clinical advisors were asked what the relevant comparator would be in Aotearoa. They were then asked to consider whether it was likely to score ESMO-MCBS A, B, 4 or 5 when compared against the relevant comparator. Where the advisors expressed conflicting views, consensus was sought through further discussion. Based on the clinical advice provided, additional clinical trial evidence from the literature was reviewed, and the results (where available) were used to validate the estimated 'Aotearoa-relevant' ESMO-MCBS score for those medicine-indication pair gaps where needed.

For medicine-indication pair gaps for which the ESMO-MCBS score was A, B, 4 or 5 (or likely to be so), further input from the advisory group was sought. Advisors were asked to confirm the relevance of the ESMO-MCBS score in the Aotearoa clinical context.

Through this process, each medicine-indication pair was categorised as one of the following:

- Gap – substantial clinical benefit (ie, ESMO-MCBS score A, B, 4 or 5 or likely to be so)
- Gap – not substantial clinical benefit (ie, ESMO-MCBS score unlikely to be A, B, 4 or 5)
- Gap – uncategorised (ie, unable to estimate a relevant ESMO-MCBS score)
- Not a gap (ie, same access in both Australia and Aotearoa).

For gaps associated with substantial clinical benefit and where there was more than one equivalent option for a given indication (such as multiple options within the same drug class), these were considered as a single gap.

Assessment of gaps for haematological malignancies (blood cancers)

As previously described, formal gap categorisation based on ESMO-MCBS was not able to be performed for blood cancer medicines. However, where a preliminary score had been calculated by EHA, this was provided. Furthermore, current Pharmac status was documented.

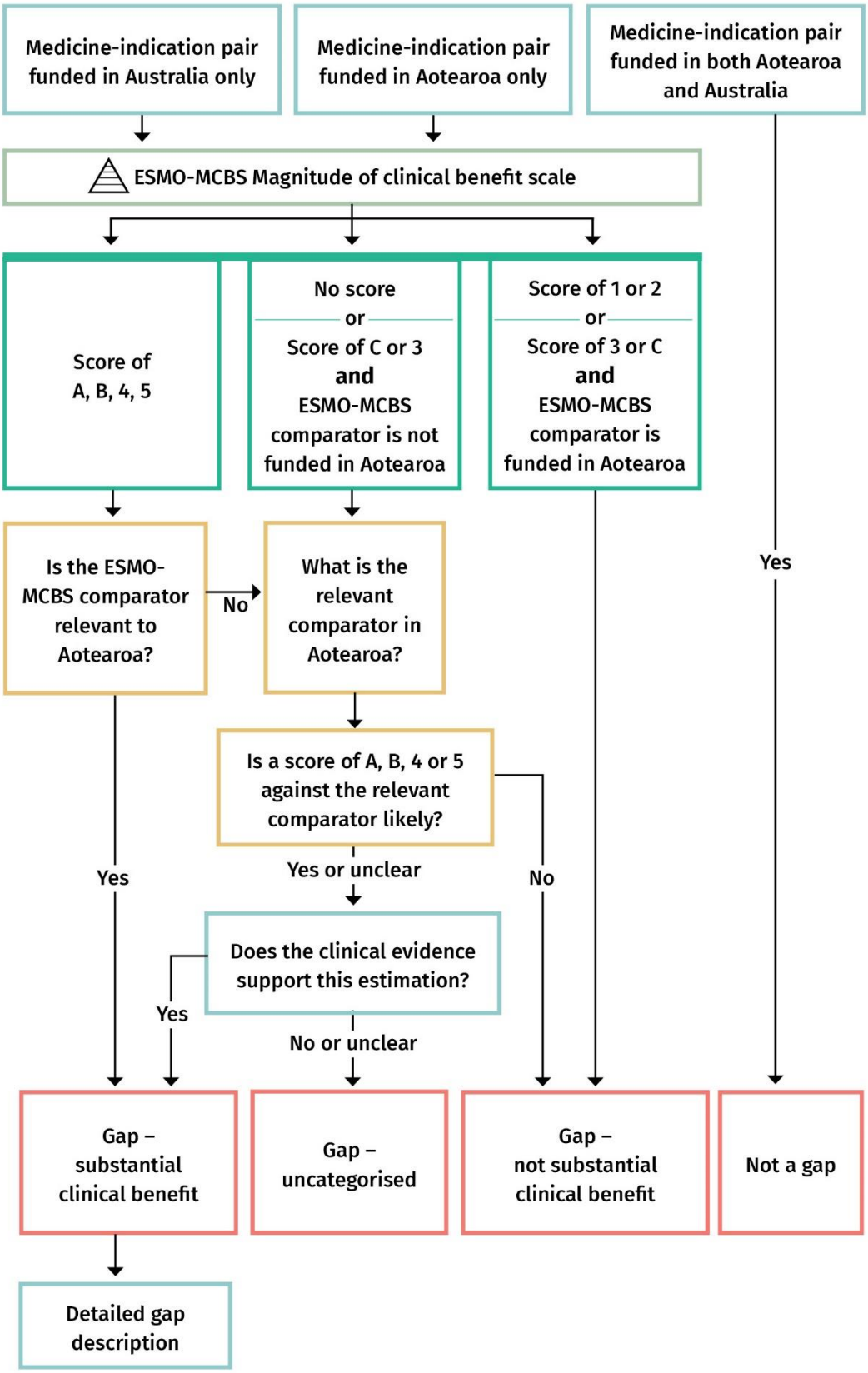
Description of gaps for medicines for solid tumours associated with substantial clinical benefit

For each gap categorised as having likely substantial clinical benefit in the Aotearoa setting, additional information was collated, including:

- a description of the clinical benefit informing the ESMO-MCBS categorisation
- a description of how addressing the gap might change current clinical practice
- an estimation of the eligible patient population, based largely on Pharmac assessments, where this information was available
- the associated health system requirements if gaps were funded, for example, additional clinic visits, infusion capacity and associated molecular testing
- associated patient considerations, such as longer or shorter treatment times, travel requirements and side effects.
- an epidemiological description of the relevant cancer, including incidence, mortality, survival and inequities across each of these

Figure 2 illustrates the process described above.

Figure 2: Process for comparing solid tumour cancer medicines' availability in Aotearoa and Australia



Comparison with Ontario, Canada

The list of medicine-indication pair gaps in Aotearoa that were likely to offer substantial clinical benefit was then checked against their funding status in Ontario, Canada. An initial comparison was completed by an oncology pharmacist practicing in Ontario, with additional assessment and clarification using the Cancer Care Ontario Drug Formulary (Cancer Care Ontario nd). Medicine-indication pairs were then categorised as not funded, funded (universally) or funded (not universally).

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RESULTS

Comparison with the World Health Organization's Essential Medicines List

There were 160 medicine-indication pairs identified by the WHO as essential for cancer treatment. Of these, the vast majority are funded in Aotearoa, in many cases with no restriction on the indication for the medicine.

Three medicine-indication pairs were identified as not funded in Aotearoa: afatinib for lung cancer, asparaginase for lymphoid leukaemia (a blood cancer) and realgar-indigo naturalis formulation for acute myeloid leukaemia (a blood cancer). After seeking clinical advice, these were not considered to be true gaps as there were equivalent or superior funded alternatives identified for each scenario (see Table 2). Further detail is provided in Appendix 2, Table 2.1.

Table 2: Assessment of differences between Aotearoa and WHO-EML

Medicine	Indication specified in WHO-EML	Therapeutic option funded in Aotearoa
Afatinib	Other specified malignant neoplasms of bronchus or lung	Erlotinib, gefitinib
Asparaginase	Lymphoid leukaemia, not otherwise specified	Pegaspargase
Realgar-indigo naturalis formulation	Acute myeloid leukaemia with recurrent genetic abnormalities	Arsenic trioxide

Comparison with Australia's Pharmaceutical Benefits Scheme

There were 140 different cancer medicines (including for blood cancers) that were funded in either or both Aotearoa and Australia. These medicines represented more than 200 medicine-indication pairs.

Medicines funded in both jurisdictions (solid tumour and blood cancer medicines)

Seventy-one individual cancer medicines were identified as being funded in both Aotearoa and Australia. These medicines are likely to represent a large number of medicine-indication pairs. It was not practical to count these with precision given that over one-third of the medicines are funded in both jurisdictions without specified indication restrictions. For example, cyclophosphamide is funded without restriction in both Aotearoa and Australia and is included in roughly 100 different treatment regimens across roughly 15 different tumour types (Cancer Institute NSW nd-b). A list of the medicines funded in both jurisdictions is presented in **Appendix 3, Table 3.1**.

Medicines funded in Aotearoa and not in Australia (solid tumour and blood cancer medicines)

Fourteen individual cancer medicines were funded in Aotearoa but not included in the Australian PBS schedule, with the majority funded without restrictions. It is important to note that, due to differences in funding arrangements between Aotearoa and Australia, some of the identified gaps in Australia are likely available through public funding mechanisms that sit outside the PBS. A list of the medicines funded in Aotearoa and not in Australia via the PBS is presented in **Appendix 4, Table 4.1**.

Medicines funded in Australia and not in Aotearoa (solid tumour and blood cancer medicines)

Seventy-two individual cancer medicines were identified as either being funded in Australia and not in Aotearoa or funded in Aotearoa as well as Australia but not for the specific indication. These 72 medicines represented 126 medicine-indication pairs, including for haematology cancer indications and taking into account likely indications (based on TGA approval and eviQ guidelines) for the small number of medicines funded in Australia without restriction. Of the 126 medicine-indication pair gaps identified, 28 pairs were for blood cancers, and the remaining 98 were for solid tumours. After adjusting for medicines used in combination, there was a total of 88 medicine-/regimen-indication pair gaps for solid tumours, and 26 for blood cancers. Lists of the medicines funded in Australia and not in Aotearoa, according to ESMO-MCBS score category are presented in **Appendix 5, Tables 5.1–5.7**.

Blood cancer medicines funded in Australia and not in Aotearoa

Of the 28 medicine-indication pair gaps for blood cancers, once adjustments were made for medicines used in combination, there was a total of 26 medicine/regimen-indication pair gaps. Of these 26 gaps, 12 had no EHA/ESMO preliminary ESMO-MCBS score available (Kiesewetter et al 2020). Seven gaps had preliminary scores that would indicate likely substantial clinical benefit (ie, A, B, 5 or 4). The remaining seven gaps had preliminary scores that would indicate substantial clinical benefit is unlikely (ie, C, 3, 2 or 1). Details of these results are presented in **Appendix 5, Table 5.7**.

Solid tumour medicines funded in Australia and not in Aotearoa

Of the 98 medicine-indication pair gaps for solid tumours, once adjustments were made for medicines used in combination, there was a total of 88 medicine/regimen-indication pair gaps. Lists of the medicines funded in Australia and not in Aotearoa, according to ESMO-MCBS score category are presented in **Appendix 5, Tables 5.1–5.6**.

Gaps associated with substantial clinical benefit – curative setting[8]

Four medicine-indication pair gaps were identified that had an ESMO-MCBS score of A. No gaps with a score of B were identified. An additional medication-indication pair gap in the curative setting was identified as 'no score available' but considered likely to be scored at least B. After adjustments for regimens (where more than one medicine must be used in combination) and accounting for multiple options to fill certain gaps, **the total number of gaps associated with substantial clinical benefit in the curative setting was three – one for early breast cancer and two for melanoma.** These gaps are discussed below and described in more detail in **Appendix 7**.

[8] An ESMO-MCBS score of A or B indicates a medicine-indication pair associated with substantial clinical benefit and used with curative intent. Curative intent treatments are used with the intent of curing the disease. The medicines are usually used in combination with surgery and/or radiotherapy – they are given with the intention of stopping a tumour that was treated from recurring.

Gaps associated with substantial clinical benefit – non-curative setting[9]

A total of nine medicine-indication pair gaps were identified that had an ESMO-MCBS score of 5, and 26 were identified with an ESMO-MCBS score of 4. A further three medicine-/regimen-indication pair gaps with either an ESMO-MCBS score of 3 or no score were categorised as likely to score at least 4 in the Aotearoa clinical context based on the clinical literature (see also **Appendix 5, Tables 5.4 and 5.6** and **Appendix 7**). After adjusting for regimens (where more than one medicine must be used in combination) and accounting for multiple options to fill certain gaps, **a total of 17 gaps associated with substantial benefit in the non-curative setting were identified.** These gaps covered eight cancer types: lung (five gaps), bowel (two gaps), liver (one gap), kidney (three gaps), bladder (one gap), ovarian (two gaps), head and neck (one gap), and skin (two gaps). These gaps are discussed below and described in more detail in **Appendix 7**.

There were four gaps for which a likely score relevant to Aotearoa could not be determined – these gaps were not further analysed.

Gaps associated with substantial clinical benefit – results by tumour type

Lung cancer gaps

Five gaps in medicines (or combinations of medicines) for lung cancer were defined by ESMO-MCBS as likely to have substantial clinical benefit. These are summarised in **Table 3**, with further detail presented in **Appendix 7, Tables 7.1–7.5**.

[9] An ESMO-MCBS score of 5 or 4 indicates a medicine-indication pair associated with substantial clinical benefit in the non-curative setting. Non-curative intent treatments are not used with the intent of curing the disease; instead, they are used with the intention of increasing the duration and/or quality of a person's remaining life living with the cancer. Medicines used in this setting may be used alone, or alongside palliative surgery or radiotherapy.

Table 3: Lung cancer gaps

Indication	Medicine/regimen	ESMO-MCBS	Pharmac status at time of analysis	Appendix table for further detail
Non-small cell lung cancer Locally advanced or metastatic, first-line therapy (regardless of PD-L1 status*)	Atezolizumab with bevacizumab (with chemotherapy) OR	Not available	Recommended for decline[10]	7.1
	Nivolumab with ipilimumab (with chemotherapy) OR	4	No application received	
	Pembrolizumab (with or without chemotherapy)	5	Ranked as an option for investment[11]	
Non-small cell lung cancer Locally advanced or metastatic, second-line therapy	Atezolizumab OR	5	Ranked as an option for investment[12]	7.2
	Nivolumab	5	Ranked as an option for investment[13]	
Non-small cell lung cancer Stage III, consolidation after chemoradiotherapy	Durvalumab	4	Ranked as an option for investment[14]	7.3
Non-small cell lung cancer Stage IIIb or IV, EGFR +ve, first-line therapy	Osimertinib	4	Under assessment – not yet ranked	7.4
Non-small cell lung cancer Stage IIIb or IV, EGFR +ve with T790M mutation, second-line therapy	Osimertinib	4	Under assessment – not yet ranked	7.5

* In clinical trials, the regimens used and clinical efficacy differed based on PD-L1 status of the lung cancer. Pharmac has active funding applications both with and without regard to PD-L1 status. In Australia, these medicines are funded without guidance regarding PD-L1 status, and therefore this analysis considered both 'PD-L1 high' and 'all comers' together as one group.

[10] At time of publication this status had been updated to 'seeking clinical advice'. See Appendix 7, Table 7.1 for details.

[11] At time of publication this status had been updated to 'seeking clinical advice'. See Appendix 7, Table 7.1 for details.

[12] At time of publication this status had been updated to 'seeking clinical advice'. See Appendix 7, Table 7.2 for details.

[13] At time of publication this status had been updated to 'seeking clinical advice'. See Appendix 7, Table 7.2 for details.

[14] At time of publication this status had been updated to 'seeking clinical advice'. See Appendix 7, Table 7.3 for details.

None of the gaps in lung cancer were in settings where the medicines would be used with the aim of curing the disease. All gaps were in non-small cell lung cancer, generally for treatment at locally advanced or metastatic stages, and were across both first and second lines of therapy. There were seven medicines represented by these gaps: some medicines were used in combination; in some instances, there were multiple medicines that could address the same gap; and in other cases, filling one gap would make another gap redundant.

Lung cancer is one of the most commonly diagnosed cancers in Aotearoa, with 2,381 people diagnosed in 2018 (including 507 Māori) and 1,781 deaths in 2017 (including 368 Māori) (Te Aho o Te Kahu 2021a). Non-small cell lung cancer makes up about 70 percent of all lung cancers (Stevens et al 2007; Te Aho o Te Kahu 2021b). A study in Aotearoa found that 22.5 percent of patients with non-small cell lung cancer who were tested for EGFR mutations between 2010 and 2017 were EGFR-mutation positive, with higher rates of EGFR mutation-positive disease in Pacific peoples, Asian populations and Māori (Aye et al 2021). Over half of all people diagnosed with lung cancer are diagnosed at a locally advanced or metastatic stage (Gurney, Stanley, Jackson, et al 2020), when surgical resection or radical chemoradiation is not a feasible option. Lung cancer incidence as a whole is more than three times higher in Māori compared with non-Māori and nearly two times higher in Pacific peoples compared with non-Māori non-Pacific non-Asian peoples. Overall, lung cancer has a five-year survival rate of 19 percent (Te Aho o Te Kahu 2021a). From 2007-2016 data, Māori with lung cancer were 30 percent more likely to die than non-Māori with lung cancer, with survival disparities present across all stages of disease at diagnosis (Gurney, Stanley, McLeod, et al 2020).

The size of the population that would benefit if the gaps in non-small cell lung cancer medicine funding were filled ranges from likely <100 to 900 people per year (see Appendix 7). The magnitude of benefit ranges from a progression-free survival gain of about 1.5 months (for atezolizumab with bevacizumab as first-line therapy) to an overall survival gain of 18.4 months (for durvalumab). **Subsequent to the completion of this analysis, Pharmac has approved durvalumab for funding in this treatment setting, and therefore this gap will now be filled** (Pharmac 2022b).

Breast cancer gap

There was one gap in medicines for breast cancer that was likely to have substantial clinical benefit. This was trastuzumab emtansine for early stage HER-2+ breast cancer, an adjuvant therapy used after primary treatment (surgery), with the intent to cure. Although there was no ESMO-MCBS score available for trastuzumab emtansine, it is likely to be categorised as A/B based on 11 percent gain in invasive disease-free survival at three years compared with trastuzumab, albeit with a poorer toxicity profile (von Minckwitz et al 2018). Further detail is presented in Appendix 7, Table 7.6.

Table 4: Breast cancer gap

Indication	Medicine/regimen	ESMO-MCBS	Pharmac status at time of analysis	Appendix table for further detail
Early stage, HER-2 +ve, adjuvant to surgery and neo-adjuvant trastuzumab and chemotherapy, with residual disease	Trastuzumab emtansine	Not available	Ranked as an option for investment	7.6

Breast cancer is the second most commonly diagnosed cancer in Aotearoa, with an average of 3,000 women, including 400 Māori (Te Aho o Te Kahu 2021a), and around 25 men diagnosed each year (Breast Cancer Foundation New Zealand 2022). The incidence of breast cancer as a whole is 1.2 times higher in Māori compared with non-Māori and slightly higher in Pacific peoples compared with non-Māori non-Pacific non-Asian peoples (Te Aho o Te Kahu 2021a). Early-stage breast cancer includes ductal carcinoma in situ as well as breast cancers in stages I, II and IIIa. Around 80 percent of women with breast cancer are diagnosed with either stage I or stage II disease, lower for Pacific peoples (70 percent). About 13 percent of women with breast cancer are diagnosed with stage III disease, with this being higher for Māori (14 percent) and Pacific peoples (19 percent). Approximately 15 percent of women with breast cancer will be HER2+, significantly higher for Pacific women (24 percent). Around 91 percent of those diagnosed with invasive breast cancer (defined as stage I disease or higher) will survive to five years (89 percent for Māori, 87 percent for Pacific peoples). By stage of disease, data from the New Zealand Breast Cancer Register indicates that 99 percent of patients diagnosed with Stage I, 93 percent of those with Stage II, and 81 percent of those with Stage III will survive to five years. From 2003–2020 data, Māori patients with breast cancer are 33 percent and Pacific are 52 percent more likely to die than non-Māori non-Pacific non-Asian peoples (Breast Cancer Foundation New Zealand 2022).

The size of the population that would benefit if this gap was funded is at least 110 people each year, reflecting the subset of the group that currently receives trastuzumab but who would be switched to trastuzumab emtansine if they had residual disease detected after surgery.

Liver cancer gap

There was one gap in liver cancer medicine funding that was defined by ESMO-MCBS as likely to have substantial clinical benefit, represented by a combination of two medicines (atezolizumab with bevacizumab). This gap was in the non-curative treatment setting, in first-line therapy for advanced hepatocellular cancer.

Table 5: Liver cancer gap

Indication	Medicine/regimen	ESMO-MCBS	Pharmac status at time of analysis	Appendix table for further detail
Hepatocellular carcinoma (HCC), advanced stage, first-line therapy	Atezolizumab with bevacizumab	5	Seeking clinical advice – not yet ranked[15]	7.7

Most primary liver cancers are hepatocellular carcinomas.[16] On average, 315 people are diagnosed with liver cancer every year, including an average of 66 Māori, and there are 234 deaths each year, including 43 Māori. The incidence of liver cancer is three times higher for Māori compared with non-Māori (Gurney, Robson et al 2020) and about four times higher for Pacific peoples compared with non-Māori non-Pacific non-Asian peoples (Te Aho o Te Kahu 2021a). More than one-third of liver cancers (34 percent Māori, 38 percent non-Māori) are diagnosed at an advanced stage (Chamberlain et al 2013). Those diagnosed with liver cancer have approximately 20 percent survival at five years (Te Aho o Te Kahu 2021a). Data from 2007-2016 showed that Māori patients with liver cancer were 31 percent more likely to die from that cancer than non-Māori patients with liver cancer. Survival disparities between Māori and non-Māori were found to be the strongest among those with either advanced or unstaged disease (Gurney, Stanley, McLeod, et al 2020).

The size of the eligible population that would benefit if this gap were funded is about 60–70 people each year, and the magnitude of benefit is (at least) an overall survival gain of 9.6 months.

[15] At time of publication this status had been updated to 'options compared'. See Appendix 7, Table 7.7 for more details.

[16] Cancers that have spread to the liver from another site are not included as liver cancers, for example, a breast cancer that has spread to the liver is still considered to be a breast cancer rather than liver cancer.

Bowel cancer gaps

There were two gaps in bowel cancer that were defined by ESMO-MCBS as likely to have substantial clinical benefit, represented by two medicine options: cetuximab and panitumumab. The gaps were both in metastatic colorectal cancer with a wild-type (non-mutated) RAS gene, in the non-curative setting. One gap was in first-line therapy and the other was in second-line therapy. If the first-line gap were filled, this would make the second-line gap redundant.

Table 6: Bowel cancer gaps

Indication	Medicine/regimen	ESMO-MCBS	Pharmac status at time of analysis	Appendix table for further detail
Colorectal cancer (CRC), metastatic, RAS wild-type, first-line therapy	Cetuximab (used with chemotherapy) OR Panitumumab (used with chemotherapy)	4 4	Ranked as an option for investment[17]	7.8
Colorectal cancer (CRC), metastatic, RAS wild-type, second-line therapy	Cetuximab (used with or without chemotherapy)	4	Under consultation for decline[18]	7.9

Colorectal cancers are the third most commonly diagnosed cancers in Aotearoa, with an average of 3,000 people diagnosed each year, including 184 Māori (Gurney, Robson, et al 2020; Te Aho o Te Kahu 2021a) and 1,230 deaths each year, including 70 Māori (Te Aho o Te Kahu 2021a). The incidence and mortality of colorectal cancer is lower for Māori and Pacific peoples (Te Aho o Te Kahu 2021a).

Around 25 percent of patients with colon or rectal cancer are diagnosed with stage IV (metastatic) disease. Māori appear to be more likely to be diagnosed with metastatic disease (29 percent colon, 29 percent rectal) than non-Māori non-Pacific peoples (22 percent colon, 18 percent rectal) (Jackson et al 2015). About 10 percent of people with advanced disease will survive to five years (Araghi et al 2021). Based on data from 2007–2016, Māori patients with colorectal cancer are more likely to die from their cancer than non-Māori patients with colorectal cancer (colon: 46 percent more likely; rectal: 72 percent more likely) (Gurney, Stanley, McLeod, et al 2020).

The size of the eligible population that would benefit if this gap was filled is up to 70 people per year. The magnitude of benefit ranges from an overall survival gain of 4.7 months (for cetuximab in second-line therapy) to 8.2 months (for cetuximab in first-line therapy).

[17] There are multiple funding applications related to this gap. See Appendix 7, Table 7.8 for more details.

[18] At time of publication this status had been updated to 'decision made'. See Appendix 7, Table 7.9 for more details.

Kidney cancer gaps

There were three gaps in kidney cancer medicine funding that were defined by ESMO-MCBS as likely to have substantial clinical benefit, represented by three medicines. All the gaps were for stage IV renal cell carcinoma of the clear cell variant, across both first and second lines of therapy, and in the non-curative setting.

Table 7: Kidney cancer gaps

Indication	Medicine/regimen	ESMO-MCBS	Pharmac status at time of analysis	Appendix table for further detail
Renal cell carcinoma (RCC), clear cell variant, stage IV, first-line therapy	Nivolumab with ipilimumab	4	No application received	7.10
Renal cell carcinoma (RCC), clear cell variant, stage IV, second-line therapy	Nivolumab	5	Ranked as an option for investment	7.11
Renal cell carcinoma (RCC), clear cell variant, stage IV, second-line therapy	Axitinib	4	Ranked as an option for investment	7.12

Most kidney cancers are renal cell cancers. An average of 540 people are diagnosed with kidney cancer each year, including 60 Māori. There are 190 deaths each year from kidney cancer, including 19 Māori (Gurney, Robson, et al 2020; Te Aho o Te Kahu 2021a). The incidence of kidney cancer is 1.4 times higher for Māori compared with non-Māori (Te Aho o Te Kahu 2021a) but lower for Pacific peoples compared with non-Maori non-Pacific non-Asian peoples (Meredith et al 2012). About one-quarter of kidney cancers are diagnosed at an advanced stage, the closest approximation to Stage IV disease (22 percent total, 25 percent Māori, 22 percent European). Around 20 percent remain unstaged on the New Zealand Cancer Registry (19 percent total, 28 percent Māori, 19 percent European) (Gurney, Stanley, Jackson et al 2020). Around two-thirds of those diagnosed with kidney cancer will survive to five years after diagnosis (62 percent Māori, 68 percent non-Māori) (Gurney, Stanley, McLeod, et al 2020). From 2007 to 2016 data, Māori patients with kidney cancer are 63 percent more likely to die from that cancer than non-Māori patients with kidney cancer. There is currently a lack of robust stage-specific survival data for kidney cancer in Aotearoa.

The size of the eligible population is likely to be under 95 people per year (see calculations in Appendix 7) for first-line therapy, and for second-line therapy, estimated at 120 people in the first year and about 60 people per year thereafter. The magnitude of benefit ranges from an overall survival gain of 0.9 months (for axitinib as second-line therapy) to 21.5 months (for nivolumab with ipilimumab as first-line therapy).

Bladder cancer gaps

There was one gap bladder cancer that was defined by ESMO-MCBS as likely to have substantial clinical benefit, represented by one medicine (pembrolizumab) with an ESMO-MCBS score of 4. The gap was in locally advanced or metastatic urothelial cancers, as second-line therapy in the non-curative setting.

Table 8: Bladder cancer gap

Indication	Medicine/regimen	ESMO-MCBS	Pharmac status at time of analysis	Appendix table for further detail
Urothelial cancer, locally advanced or metastatic, second-line therapy	Pembrolizumab	4	Ranked as an option for investment	7.13

Each year, an average of 380 people are diagnosed with bladder cancer (of which the vast majority are urothelial cancers), including 24 Māori (Te Aho o Te Kahu 2021a). On average over the last decade, there have been 202 deaths each year from bladder cancer, including 11 Māori (Gurney, Robson, et al 2020; Te Aho o Te Kahu 2021a). The incidence of bladder cancer is somewhat lower for Māori compared with non-Māori (Robson et al 2010) and similarly lower for Pacific peoples compared with non-Māori non-Pacific non-Asian peoples (Meredith et al 2012).

There is currently a lack of national, robust staging information available for bladder cancer in Aotearoa, and the vast majority of bladder cancers remain unstaged on the New Zealand Cancer Registry (70 percent of total cases, 65 percent Māori, 66 percent European). Approximately 12 percent are listed on the New Zealand Cancer Registry as having advanced disease, with the remaining 18 percent listed as having either local (7 percent) or regional (11 percent) disease (Gurney, Stanley, Jackson, et al 2020). Around half of those diagnosed with bladder cancer will survive to five years post diagnosis (43 percent Māori, 52 percent non-Māori) (Gurney, Stanley, McLeod, et al 2020). There is currently a lack of robust stage-specific survival data for bladder cancer in Aotearoa. From 2007–2016 data, Māori patients with bladder cancer are 37 percent more likely to die from their cancer than non-Māori patients with bladder cancer (Gurney, Stanley, McLeod, et al 2020).

The size of the eligible population is estimated at 50 people each year, and the magnitude of benefit from pembrolizumab for this indication is an estimated overall survival gain of 2.9 months, with fewer serious adverse events compared with chemotherapy.

Ovarian cancer gaps

There were two gaps in medicines for ovarian cancer that were defined by ESMO-MCBS as likely to have substantial clinical benefit (olaparib and bevacizumab). These are summarised in Table 9, with further detail presented in Appendix 7, Tables 7.14 and 7.15.

Table 9: Ovarian cancer gaps

Indication	Medicine/ regimen	ESMO-MCBS	Pharmac status at time of analysis	Appendix table for further detail
Epithelial ovarian, fallopian tube or primary peritoneal cancer, stage IIIb or IV, BRCA +ve, first-line maintenance	Olaparib	4	Ranked as an option for investment[19]	7.14
Epithelial ovarian, fallopian tube or primary peritoneal cancer, metastatic, recurrent platinum-resistant	Bevacizumab	4	Under consultation for decline[20]	7.15

Both gaps were for late-stage ovarian cancer in the non-curative setting, and one (olaparib) was for a particular mutation called BRCA. Pharmac has recently consulted on a proposal to decline bevacizumab and, based on feedback received, will now seek further clinical advice. **Subsequent to the completion of this analysis, Pharmac has approved olaparib for funding in this treatment setting, and therefore this gap will now be filled – at least in part – for those with germline BRCA mutations (Pharmac 2022b).**

An average of 280 people are diagnosed with ovarian cancer each year, including 32 Māori, and there are about 194 deaths each year, including 15 Māori (Gurney, Robson, et al 2020; Te Aho o Te Kahu 2021a). The incidence of ovarian cancer is somewhat higher for Māori compared with non-Māori (Robson et al 2010), and it is also higher among Pacific peoples compared with non-Māori non-Pacific non-Asian peoples (Meredith et al 2012). International studies have shown that about 10-20 percent of epithelial ovarian cancer patients are germline BRCA positive (Alsop et al 2012, Zhang et al 2011).

Nearly two-thirds of ovarian cancers are diagnosed at an advanced stage (60 percent of total cases, 58 percent Māori, 63 percent European). Around 40 percent of those diagnosed with ovarian cancer will survive five years after diagnosis (43 percent Māori, 39 percent non-Māori) (Gurney, Stanley, McLeod, et al 2020). There is currently a lack of robust stage-specific survival data for ovarian cancer in Aotearoa, although one study found that around 20 percent of patients with advanced disease survived to five years (Yeoh et al 2019). From 2007–2016 data, Māori patients with ovarian cancer are 62 percent more likely to die than non-Māori patients with ovarian cancer (Gurney, Stanley, McLeod, et al 2020).

[19] At time of publication this status had been updated to 'approved for funding'. See Appendix 7, Table 7.14 for details.

[20] At time of publication this status had been updated to 'seeking clinical advice'. See Appendix 7, Table 7.15 for more details.

The size of the eligible population was unable to be estimated for bevacizumab, although it is likely to be small considering this is a very specific subset of patients. The eligible population for olaparib is approximately 20 people in the first year and then increasing over time. The magnitude of benefit ranges from a progression-free survival gain of 3.3 months for bevacizumab to over 30 months for olaparib.

Head and neck cancer gap

There was one gap in head and neck cancer medicine funding that was defined by ESMO-MCBS as likely to have substantial clinical benefit, represented by one medicine (nivolumab), with an ESMO-MCBS score of 5. The gap was in locally recurrent or metastatic head and neck squamous cell cancer as second-line therapy in the non-curative setting.

Table 10: Head and neck cancer gap

Indication	Medicine/regimen	ESMO-MCBS	Pharmac status at time of analysis	Appendix table for further detail
Head and neck squamous cell cancer (HNSCC), locally recurrent or metastatic, second-line therapy	Nivolumab	5	No application received	7.16

An average of 550 people are diagnosed with head and neck cancer each year, including 55 Māori (Te Aho o Te Kahu 2021a), and there are about 170 deaths from this cancer each year, including 17 Māori (Gurney, Robson, et al 2020; Te Aho o Te Kahu 2021a). The incidence of head and neck cancer is similar for Māori and non-Māori but appears to be higher among Pacific peoples compared with non-Māori non-Pacific non-Asian peoples (Te Aho o Te Kahu 2021a).

The majority of head and neck cancers are diagnosed at either the local or regional stage. While the New Zealand Cancer Registry records less than 10 percent of head and neck cancer patients as being diagnosed with advanced disease (7 percent total, 9 percent Māori, 6 percent European), more than one-third of diagnoses remain unstaged on the registry (37 percent total, 42 percent Māori, 36 percent European) (Gurney, Stanley, Jackson, et al 2020). Around two-thirds of those diagnosed with head and neck cancer will survive to five years after diagnosis (64 percent Māori, 64 percent non-Māori) (Soeberg et al 2012). There is currently a lack of robust stage-specific survival data for head and neck cancer in Aotearoa. Based on estimates from 2001–2004, Māori head and neck cancer patients had 37 percent greater excess mortality than non-Māori patients (Soeberg et al 2012).

The size of the eligible population was unable to be estimated, and the magnitude of benefit is an overall survival gain of 2.4 months.

Melanoma skin cancer gaps

There were four gaps in medicines funding for skin cancer that were defined by ESMO-MCBS as likely to have substantial clinical benefit. Two gaps were in the curative setting and two in the non-curative setting. All the gaps were in stage III or IV melanoma, and additionally two of the gaps were for a particular tumour mutation called BRAF. There were nine medicines represented by these gaps: some medicines were used in combination, and in some instances, there were multiple medicines that could address the same gap.

Table 11: Skin cancer gaps

Indication	Medicine/regimen	ESMO-MCBS	Pharmac status at time of analysis	Appendix table for further detail
Melanoma, stage III (or IV), adjuvant to surgery – curative intent	Nivolumab OR Pembrolizumab	A	No application received Application deferred (not yet ranked)[21]	7.17
Melanoma, stage III, BRAF +ve adjuvant to surgery – curative intent	Dabrafenib with trametinib	A	No funding application received	7.18
Melanoma, stage III or IV, unresectable, 1st line (induction) – non-curative intent	Nivolumab with ipilimumab	Not available	Ranked as an option for decline	7.19
Melanoma, stage III or IV, BRAF +ve, unresectable, 1st line – non-curative intent	Encorafenib with binimetinib OR Vemurafenib with cobimetinib OR Dabrafenib with trametinib	4 4 5	No application received	7.20

[21] At time of publication this status had been updated to 'under assessment'. See Appendix 7, Table 7.17 for more details.

Melanoma skin cancers are the fourth most common cancers diagnosed in Aotearoa, with an average of 2,400 people diagnosed each year, including 46 Māori (Te Aho o Te Kahu 2021a). The incidence of melanoma is over five times higher for non-Māori (primarily Europeans) compared with Māori. Similarly, the incidence of melanoma is considerably lower among Pacific peoples (Meredith et al 2012). The vast majority of melanomas are diagnosed at a local stage. The gaps in the analysis apply to stage III and IV melanoma, and it is estimated that about 9 percent of all melanomas (about 216 people) are diagnosed at these stages (Gurney, Stanley, Jackson, et al 2020). Melanomas harbour BRAF mutations in 40–50 percent of cases (Greaves et al 2013; Wolfe et al 2021), although a small New Zealand study found a lower prevalence of 33 percent (Jones et al 2016). More than 80 percent of those diagnosed with melanoma will survive five years after diagnosis (80 percent Māori, 89 percent non-Māori) (Gurney, Stanley, McLeod, et al 2020). From 2007–2016 data, Māori patients with melanoma are 2.5 times more likely to die from their cancer than non-Māori patients – however, this disparity must be considered alongside the relative rarity of Māori death from melanoma (Gurney, Stanley, McLeod, et al 2020). There is currently a lack of robust stage-specific survival data for melanoma in Aotearoa.

The size of the population that would benefit if these funding gaps were removed was unable to be estimated. The magnitude of benefit from gaps in the curative setting range from a relapse-free survival gain at one year of 9.7 percent to a relapse-free survival gain at three years of 19 percent. In the non-curative setting, the magnitude of benefit ranged from a median overall survival gain of 4.9 months to 18.4 months.

Comparison with Ontario, Canada

Of the 20 solid tumour gaps associated with substantial clinical benefit in the curative and non-curative setting, 12 were universally funded in Ontario (one in a later line of treatment than is funded in Australia), seven were funded but only for people meeting certain demographic eligibility criteria (for example, being aged 65 years or older), and one was not funded. Further detail is provided in Appendix 6, Table 6.1.

HE KŌRERO
DISCUSSION

Cancer medicines are an integral part of cancer care. A diagnosis of cancer can be life changing and challenging, and people with cancer and their whānau understandably place significant hope in cancer medicines. There are strong expectations from the health sector and the public about the availability of cancer medicines. The purpose of this analysis was to better understand this complex and challenging aspect of cancer care in Aotearoa.

Summary of main findings

This analysis quantitatively showed that there are fewer cancer medicines funded in Aotearoa compared with Australia – both for solid tumours and for blood cancers - in keeping with other studies that compared Aotearoa with a range of high-income countries (Babar et al 2019; Cheema et al 2012; Evans et al 2016; Lichtenberg 2021; Wonder and Fisher 2016; Wonder and Milne 2011). However, this analysis aimed to go beyond numerical tallies of cancer medicines to consider the magnitude of (potentially foregone) clinical benefit associated with gaps in cancer medicines funding.

In terms of the comparison with the WHO Essential Medicines List, no substantive gaps were revealed. This is as would be expected for a high-income country. We can be confident that, at a minimum, the cancer medicines deemed by the WHO to be essential for all countries are available to the people of Aotearoa. In terms of the comparison with Australia, 20 medicine-indication gaps across nine solid tumour cancer types (lung, breast, bowel, liver, kidney, bladder, ovarian, melanoma, and head and neck) were identified that are likely to be significant, based on ESMO-MCBS scores indicating substantial clinical benefit. There are likely to be other significant gaps for blood cancers. Of the 20 gaps identified for solid tumours, the vast majority were in the non-curative setting, meaning that the medicines would not be used with the aim of curing the cancer but rather used with the intent of prolonging life and/or improving the quality of a person's remaining life. For several cancers, there were multiple gaps: five gaps in lung cancer, four in melanoma, three in kidney cancer and two in ovarian cancer. In some cases, funding a gap in an earlier line of treatment would make a gap in a later line redundant. The majority of the gaps identified in the comparison with Australia were also funded in Ontario, Canada – at least to some extent. This indicates that Australia is not an outlier when it comes to cancer medicines availability.

The unfunded medicines represented by the gaps were all targeted cancer therapies, as distinct from traditional chemotherapy. For two of the 20 gaps, medicines to fill them have now been approved by Pharmac for funding (Pharmac, 2022b). At time of publication, six of the 20 identified gaps had relevant medicines to fill the gaps ranked on Pharmac's Options for Investment list. For six gaps, the relevant medicines are in the process of being assessed for funding; for two gaps, medicines have either been declined or recommended for decline; and Pharmac has not received funding applications for the remaining four gaps.

The magnitude of clinical benefit was able to be defined in terms of median overall survival gain for 14 of the 20 gaps (ranging from about one month to almost 22 months) and described in terms of median disease-free survival or progression-free survival gains for the remaining six gaps (ranging from 1.5 months to over 30 months). Overall survival is universally recognised as the 'gold standard' primary end point to assess the outcome of any drug or intervention in oncology clinical trials, providing evidence that a given treatment extends the life of a patient. Quality of life, when assessed with validated scales, is also a clinically meaningful measure of benefit. Disease-free survival is used in trials conducted in the curative setting and refers to the time from when curative treatment has finished to cancer recurrence or death from any cause. Progression-free survival is a similar concept but is used in the non-curative setting – it refers to the time from randomisation or treatment initiation to the point where there is disease progression or death. Although progression-free survival is now the most commonly used primary end point in oncology clinical trials, there are concerns about its use as a surrogate for overall survival or quality of life and whether it represents clinically meaningful benefit for patients (Booth and Eisenhauer 2012, Gyawali et al 2022, Haslam et al 2019, Hwang and Gyawali 2019).

It should be noted that, although there are fewer cancer medicines funded in Aotearoa compared with Australia, once medicines are listed in Pharmac's Pharmaceutical Schedule, there is greater universal availability of those medicines. There are no inter-jurisdiction differences or differences by public cancer treatment settings, and out-of-pocket costs are also significantly lower in Aotearoa.

Context matters for gaps in cancer medicine funding

It is essential to consider these identified gaps within their wider context. Each gap sits within a cancer type or subtype that has its own distinct pattern of incidence, stage distribution, survival and mortality – as well as existing inequities in each of these areas. For example, five of the 20 gaps are for lung cancer, which is distinctive for its high incidence, high mortality, poor survival and disproportionate impact on Māori and Pacific peoples. Also relevant is what treatment options currently exist for patients. In some instances, the medicines would fill an identified gap where no funded active treatment option currently exists. In other instances, they are a superior substitute for an existing funded treatment and in still others, they are added to existing therapy or provide an additional line of therapy. These contextual factors are outlined by tumour type in the previous section, and in greater detail in Appendix 7.

Te Tiriti o Waitangi responsibilities and cancer medicines

The principles of Te Tiriti provide guidance on the role of medicines in cancer. Cancer is an area of health where inequities between Māori and non-Māori are prominent. The *Hauora* report (Waitangi Tribunal 2019) proposes the following five principles to drive future health care delivery:

- Tino rangatiratanga – the rights of Māori to exercise self-determination in the design, delivery and monitoring of health care for Māori
- Equity – the right to equitable access to health care and outcomes
- Active protection – including that government takes all reasonable actions to ensure Māori achieve equity and informs Māori of the impact of these actions
- Options – ensuring appropriate resourcing is allocated to ensure Māori can access both high-quality and appropriate mainstream health services and kaupapa Māori services
- Partnership – ensuring effective partnership with Māori in the design, delivery and monitoring of health care services.

This work recognises that Māori are a legitimate and critical part of decision-making (Ministry of Health 2014), and acknowledges Māori interests in decision-making about cancer medicines availability, including how cancer medicines are made accessible to Māori.

In health, the principle of equity refers to the absence of systematic differences in health that are not only avoidable but also unfair and unjust (Ministry of Health 2019b). Māori are 20 percent more likely to develop cancer than non-Māori and twice as likely to die from cancer, with poorer survival for nearly all the most common cancers (Gurney, Stanley, McLeod, et al 2020). These inequities are even more stark for specific cancers, such as lung cancer. They also occur along every step of the cancer continuum; for example, Māori have higher exposure to cancer risk factors, poorer access to and through the health system, and consequently poorer outcomes (Gurney, Stanley, McLeod, et al 2020; Tin Tin et al 2018; Walsh and Grey 2019). Available and accessible cancer medicines are one of many tools needed to address these inequities, and includes the consideration that Māori may require different access, approaches and resources to achieve equitable cancer outcomes (Ministry of Health 2019a).

Equity considerations for cancer medicines

The equity considerations when it comes to cancer medicines are varied and complex. In terms of the availability of cancer medicines, funding decisions must consider existing inequities in incidence, survival and mortality for the relevant cancer. Where such inequities are known for Māori and Pacific peoples, they have been included in the results section and in Appendix 7. There are likely to be similar inequities experienced by other population groups, for example, people living in deprived areas (Te Aho o Te Kahu 2021a) or people living with mental illness (Cunningham et al 2015; Davis et al 2020). The degree to which these unacceptable differences in outcomes are amenable to change through improved access to cancer medicines, and the relative priority of cancer medicines compared with other interventions to tackle these issues, differs across cancer types.

Additionally, there are other inequities that relate to eligibility for the medicine, such as inequities in stage at diagnosis or differences in the prevalence of a particular molecular subtype. Differences in factors such as stage at diagnosis may also have a meaningful influence on which medicine gaps would have a greater impact on inequities if funded. For example, if a medicine were used in early-stage disease, but we know that the majority of Māori are diagnosed later in the disease course for that particular cancer type, then there is the potential to inadvertently exacerbate inequities in outcomes for Māori. Conversely, not having the medicine available at that early stage specifically for Māori who do have an earlier diagnosis will also have a negative implication for Māori health outcomes. These matters are complex and require thorough consideration when funding applications are being assessed and decisions are being made.

Delays in availability of new effective cancer medicines in Aotearoa exacerbate inequities in outcomes as only those who can afford to pay out-of-pocket for new, non-funded medicines (or have private insurance) may be able to receive them. Conversely, although other countries may have more medicines available, higher patient co-payments may limit patients' access to these medicines (Babar et al 2019). In Australia, it was observed that a 24 percent increase in co-payments for subsidised medicines in 2005 adversely affected dispensing of prescriptions, especially among those on lower incomes (Babar and Vitry 2014; Hynd et al 2008).

Cancer medicines must be accessible, and availability is not a guarantee of accessibility

The accessibility of medicines for Māori, Pacific peoples and other population groups is influenced by many things in addition to whether they are listed in Pharmac's Pharmaceutical Schedule, including barriers of cost, time, travel and trust, as well as health system factors. Māori and Pacific peoples experience specific inequities when it comes to accessing systemic anti-cancer therapies. Examples include poorer access to trastuzumab and adjuvant chemotherapy in breast cancer (Lawrenson et al 2018, Seneviratne et al 2014), and adjuvant chemotherapy in stage III colon cancer (Hill et al 2010, Lao et al 2020).

Co-payments for prescriptions are lower in Aotearoa compared with other countries. However, cost remains a barrier to accessing and adhering to any and all prescribed medicines. Māori, Pacific peoples and those on low incomes were found to be more likely to defer purchasing a prescription at least once due to cost (Jatrana et al 2011). A qualitative study found that this can negatively impact on health directly by preventing access to medicines generally, through reducing expenditure on other items needed for health (such as nutritious food) and making changes to optimal treatment (Norris et al 2016). These findings echo those in international literature that show that older people, women, low-income populations and non-white people are among those that were most likely to report cost as a barrier. Patients also incur costs in travel for treatment and taking time off work, and such costs can be significant (Fearnley et al 2016).

Implementation of cancer medicines once funded

Many of the cancer medicine funding gaps would require additional health system resources beyond the medicines themselves and may result in additional considerations for patients. These additional considerations are outlined in detail in the tables in Appendix 7. They include medicine administration requirements, such as: infusion capacity with its associated pharmaceutical compounding, chair/bed time, medical specialist time and nursing care. For several of the gaps, molecular testing is required to determine eligibility for the medicine. Most gaps would require one or more of the following: follow-up appointments, imaging to assess disease progression, blood testing to monitor toxicities from treatment, or input from other medical specialties to address side-effects. For patients, this can mean more treatment or follow-up appointments, requiring additional time and travel. There may also be additional out-of-pocket costs such as for filling outpatient prescriptions. In short, cancer medicines do not exist in isolation but rather as part of a 'package' of cancer care. In order for the benefits of a funded medicine to be fully realised, all the components of the package need to be available and accessible, including supportive care. Importantly, they need to be available and accessible in an equitable manner.

Strengths of this analysis

The main strength of this analysis is that it goes beyond a simple comparison of the number of cancer medicines funded in Aotearoa compared with those funded in Australia. This analysis considers the specific use of the medicines (via medicine-indication pairs) and the magnitude of potential clinical benefit, using a validated and internationally recognised assessment tool, the ESMO-MCBS.

The analysis also provides important local context to the identified gaps by situating the gaps within current clinical practice in Aotearoa and within the population-level characteristics of the relevant cancer. Additionally, it includes consideration of additional health system requirements and demands on patients if the gaps were to be funded.

Interpretation of identified gaps between Aotearoa and Australia was assisted by comparing and contrasting the approach to medicines funding in both countries. Finally, this point-in-time analysis will serve as a useful baseline to review changes over time, using the same methodology.

Considerations when interpreting this analysis

There are important features and limitations of this analysis that need to be considered when interpreting its results. Firstly, this analysis was intended to consider cancer medicines availability in Aotearoa at a system or population level rather than at an individual patient level. Accordingly, there will be gaps in medicines not identified by this analysis as having substantial clinical benefit at a system or population level that may still confer significant benefit for some individuals, depending on their specific clinical circumstances.

This analysis compared medicines availability in Aotearoa with that in Australia, and that may imply that Australia is the 'gold standard' with respect to cancer medicines funding. However, no country is likely to have achieved the perfect balance of public cancer medicines funding. There may be important gaps in publicly funded cancer medicines in Australia that would not necessarily have been identified using this methodology. Furthermore, the analysis was conducted at a single point in time. The pace of change for cancer medicines is rapid, and it is likely that other cancer medicines have been funded in Australia since this analysis. For example, pembrolizumab for deficient DNA mismatch repair (dMMR) colorectal cancer, and gemtuzumab ozogamicin for acute myeloid leukaemia have both recently been approved for funding in Australia.

The ESMO-MCBS tool is internationally accepted, used by the WHO and an increasing number of guidelines groups and health technology assessment organisations internationally (ESMO nd-a; Gyawali et al 2021). However, it has its limitations and does not always correlate well with international cancer medicines funding decisions (Cheng et al 2017). The ESMO-MCBS does not specifically consider potential differences in benefits between population groups and has not been assessed from a health equity perspective. This analysis was unable to compensate for that limitation but does include known inequities in the population-level characteristics of cancers.

Another clear limitation of ESMO-MCBS is that it is not yet validated for medicines for blood cancers. We were unable to identify another appropriate tool for assessing medicines for blood cancers, but note that the European Haematology Association (EHA) and ESMO are in the process of developing one (Kiesewetter et al 2020). Blood cancers are heavily reliant on the use of medicines, given that other non-medicine options, like surgery or radiotherapy, are often not an option. We suspect that the conclusions of this analysis (which is focused on solid tumour medicines) would be similar if not more compelling for blood cancers. We plan to conduct a similar analysis for medicines used to treat blood cancers once a similarly validated tool to assess clinical benefit is available.

ESMO-MCBS scoring does not include critical appraisal of trials and assumes that clinical trials have valid research methods, appropriate data analysis and high-quality implementation. Where this is not the case, trials may produce outcomes that overstate the real benefit or are not able to be generalised and therefore skew ESMO-MCBS scores. Shortcomings in this area include the fact that ESMO-MCBS does not independently evaluate the appropriateness of the control arm and is limited in its ability to handle suboptimal crossovers, substandard post-progression treatment and publication bias in the reporting of quality-of-life outcomes. A revised version of the ESMO-MCBS is planned that aims to address some of these limitations, but that revised version was not available at the time of this analysis (ESMO 2021; Gyawali et al 2021). Additionally, the importance of considering current clinical practices when interpreting ESMO-MCBS scores has been highlighted (Cherny et al 2022) and was a central feature of this analysis.

Finally, as the ESMO-MCBS relies on findings from clinical trials, it must be acknowledged that trials are often conducted in small, tightly-defined patient populations that may not reflect people with cancer in a real-world clinical setting, where patients may be older and have more comorbidities for example. Smaller ethnic groups are under-represented in cancer clinical trials, contributing to a lack of understanding about ethnic differences in drug response or toxicity where these exist (O'Donnell and Dolan 2009).

HE KUPU WHAKAKAPI
CONCLUSION

The purpose of this analysis was to provide an objective, evidence-informed description of cancer medicines availability in Aotearoa compared with that in Australia. The funding and availability of cancer medicines is an extremely complex, fast-paced and challenging area of cancer care for all countries. It is also an area that matters deeply to people with cancer and their whānau, the health professionals that care for them and the wider public. This analysis is a first step to understanding this important issue better.

By identifying the gaps in cancer medicines and describing important context for them, we hope to provide useful insights to Pharmac, the Government, the health sector and the public. The information provided about medicine funding gaps and the associated clinical benefits of those medicines is intended to complement the other factors that Pharmac considers when it assesses medicines for funding, such as unmet need, costs and savings, and suitability. It is important to note that the statutory function of Pharmac extends beyond cancer medicines to include medicines (and increasingly medical devices) across all health conditions.

Whilst this analysis was conducted independently of Pharmac, the organisation has been aware and supportive of this work. The wider question of how much Aotearoa should spend on medicines rests with Government and must be balanced against priorities within health, as well as between health and other areas. Health systems are continually faced with decisions about how to balance investment in cancer medicines against other priorities, and there is no correct answer to the question 'How much is the right amount to spend on cancer medicines?'.

This work also informs how we can better optimise the role that cancer medicines play in improving cancer control in Aotearoa. Cancer medicines are an integral part of cancer care. However, cancer medicines do not and should not exist in isolation. Even within this analysis, it is clear that the full benefits of cancer medicines can only be realised if the 'pipeline' of cancer care (from screening and early detection through to diagnosis, staging, treatment, follow-up and supportive care) is working well and equitably. With finite resources available for health care, greater investment in cancer medicines has to be weighed against investment in the cancer workforce and infrastructure that delivers all cancer care, including medicines. Stronger cancer prevention and earlier detection are likely to be the most impactful ways to address cancer inequities for Māori and Pacific peoples.

All aspects of cancer control, from prevention to palliative care, require attention and effort. Using the resources we have in the best possible way is not easy, but it is important. Getting the right balance is essential if we are to deliver on the goals of fewer cancers, better survival and equity for all.

NGĀ ĀPITIHANGA
APPENDICES

Appendix 1: Key sources of information

This appendix lists the various key sources of information used in this analysis.

Information type	Source(s)	Link(s) (if applicable)
Medicines funded in Aotearoa	Pharmac's Pharmaceutical Schedule	https://schedule.pharmac.govt.nz/ScheduleOnline.php https://schedule.pharmac.govt.nz/HMLOnline.php
Medicines funded in Australia	PBS Schedule	www.pbs.gov.au/browse/body-system
Medicines included in the WHO-EML	WHO-EML 21st	www.who.int/publications/i/item/WHOMVPEMPIAU2019.06
Indications for medicines funded without restriction	TGA product information	www.ebs.tga.gov.au/
	eviQ	www.eviq.org.au/
	Medsafe Data Sheets	www.medsafe.govt.nz/Medicines/infoSearch.asp
ESMO-MCBS scores	ESMO	www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards
Medicines funded in Ontario, Canada	Clinical advice Cancer Care Ontario Drug Formulary	www.cancercareontario.ca/en/drugformulary/drugs
Pharmac status	Pharmac application tracker	https://connect.pharmac.govt.nz/apptracker/s/
Clinical relevance of gaps	Clinical advice ACT-NOW SACT regimen library	https://nzf.org.nz/regimens
	eviQ	www.eviq.org.au/
Patient and health sector considerations	ACT-NOW SACT regimen library	https://nzf.org.nz/regimens
	eviQ	www.eviq.org.au/
	Medsafe Data Sheets	www.medsafe.govt.nz/Medicines/infoSearch.asp

Appendix 2: Results table from the comparison with the World Health Organization's Essential Medicines List

This appendix provides results from the comparison of cancer medicines publicly funded in Aotearoa with those included in the 21st WHO-EML. For each medicine and indication listed in the WHO-EML, Table 2.1 shows whether they are publicly funded in Aotearoa.

Table 2.1: Medicines included in the WHO-EML

Medicine	Indication as per WHO-EML	Funded in Aotearoa
Abiraterone	Malignant neoplasms of prostate	Yes
Afatinib	Other specified malignant neoplasms of bronchus or lung	No (Gefitinib and erlotinib are identified by the WHO as therapeutic alternatives. Both are funded in Aotearoa for lung cancer.)
All-trans retinoic acid [tretinoin]	Acute myeloid leukaemia with recurrent genetic abnormalities	Yes
Anastrozole	Malignant neoplasms of breast	Yes
Anastrozole	Other specified malignant neoplasms of breast	Yes
Arsenic trioxide	Acute myeloid leukaemia with recurrent genetic abnormalities	Yes
Asparaginase	Lymphoid leukaemia, NOS	No (Pegaspargase has superseded this treatment in Aotearoa and is funded for acute lymphoblastic leukaemia and lymphoma.)
Bendamustine	Chronic lymphocytic leukaemia or small lymphocytic lymphoma	Yes
Bendamustine	Follicular lymphoma	Yes
Bicalutamide	Malignant neoplasms of prostate	Yes
Bleomycin	Other specified malignant neoplasms of the ovary	Yes
Bleomycin	Germ cell tumour of testis	Yes
Bleomycin	Hodgkin lymphoma	Yes
Bleomycin	Kaposi sarcoma of unspecified primary site	Yes
Bortezomib	Plasma cell myeloma	Yes
Capecitabine	Malignant neoplasms of colon	Yes

Medicine	Indication as per WHO-EML	Funded in Aotearoa
Capecitabine	Malignant neoplasm metastasis in large intestine	Yes
Capecitabine	Other specified malignant neoplasms of breast	Yes
Capecitabine	Malignant neoplasms of rectum	Yes
Carboplatin	Other specified carcinomas of ovary	Yes
Carboplatin	Other specified malignant neoplasms of bronchus or lung	Yes
Carboplatin	Osteosarcoma of bone and articular cartilage of unspecified sites	Yes
Carboplatin	Malignant neoplasms of breast	Yes
Carboplatin	Malignant neoplasms of nasopharynx	Yes
Carboplatin	Retinoblastoma	Yes
Carboplatin	Malignant neoplasms of cervix uteri	Yes
Chlorambucil	Chronic lymphocytic leukaemia or small lymphocytic lymphoma	Yes
Cisplatin	Other specified malignant neoplasms of the ovary	Yes
Cisplatin	Osteosarcoma of bone and articular cartilage of unspecified sites	Yes
Cisplatin	Germ cell tumour of testis	Yes
Cisplatin	Other specified malignant neoplasms of bronchus or lung	Yes
Cisplatin	Squamous cell carcinoma of oropharynx	Yes
Cisplatin	Malignant neoplasms of cervix uteri	Yes
Cisplatin	Malignant neoplasms of nasopharynx	Yes
Cyclophosphamide	Malignant trophoblastic neoplasms of placenta	Yes
Cyclophosphamide	Ewing sarcoma of bone and articular cartilage of unspecified sites	Yes
Cyclophosphamide	Follicular lymphoma	Yes
Cyclophosphamide	Other specified malignant neoplasms of breast	Yes
Cyclophosphamide	Lymphoid leukaemia, NOS	Yes
Cyclophosphamide	Chronic lymphocytic leukaemia or small lymphocytic lymphoma	Yes
Cyclophosphamide	Malignant neoplasms of breast	Yes
Cyclophosphamide	Rhabdomyosarcoma primary site	Yes

Medicine	Indication as per WHO-EML	Funded in Aotearoa
Cyclophosphamide	Hodgkin lymphoma	Yes
Cyclophosphamide	Plasma cell myeloma	Yes
Cyclophosphamide	Burkitt lymphoma including Burkitt leukaemia	Yes
Cyclophosphamide	Diffuse large B-cell lymphomas	Yes
Cytarabine	Burkitt lymphoma, including Burkitt leukaemia	Yes
Cytarabine	Lymphoid leukaemia, NOS*	Yes
Cytarabine	Acute myeloid leukaemia with recurrent genetic abnormalities	Yes
Cytarabine	Myeloid leukaemia	Yes
Dacarbazine	Hodgkin lymphoma	Yes
Dactinomycin	Malignant trophoblastic neoplasms of placenta	Yes
Dactinomycin	Malignant neoplasms of kidney, except renal pelvis	Yes
Dactinomycin	Rhabdomyosarcoma primary site	Yes
Dasatinib	Chronic myeloid leukaemia, NOS	Yes
Daunorubicin	Acute myeloid leukaemia with recurrent genetic abnormalities	Yes
Daunorubicin	Lymphoid leukaemia, NOS	Yes
Daunorubicin	Myeloid leukaemia	Yes
Docetaxel	Malignant neoplasms of prostate	Yes
Docetaxel	Other specified malignant neoplasms of breast	Yes
Docetaxel	Malignant neoplasms of breast	Yes
Doxorubicin	Malignant neoplasms of breast	Yes
Doxorubicin	Hodgkin lymphoma	Yes
Doxorubicin	Other specified malignant neoplasms of breast	Yes
Doxorubicin	Burkitt lymphoma including Burkitt leukaemia	Yes
Doxorubicin	Malignant neoplasms of kidney, except renal pelvis	Yes
Doxorubicin	Ewing sarcoma of bone and articular cartilage of unspecified sites	Yes
Doxorubicin	Follicular lymphoma	Yes
Doxorubicin	Osteosarcoma of bone and articular cartilage of unspecified sites	Yes
Doxorubicin	Lymphoid leukaemia, NOS	Yes

Medicine	Indication as per WHO-EML	Funded in Aotearoa
Doxorubicin	Plasma cell myeloma	Yes
Doxorubicin	Kaposi sarcoma of unspecified primary site	Yes
Doxorubicin	Diffuse large B-cell lymphomas	Yes
Erlotinib	Other specified malignant neoplasms of bronchus or lung	Yes
Etoposide	Other specified malignant neoplasms of bronchus or lung	Yes
Etoposide	Malignant trophoblastic neoplasms of placenta	Yes
Etoposide	Germ cell tumour of testis	Yes
Etoposide	Hodgkin lymphoma	Yes
Etoposide	Other specified malignant neoplasms of the ovary	Yes
Etoposide	Burkitt lymphoma, including Burkitt leukaemia	Yes
Etoposide	Ewing sarcoma of bone and articular cartilage of unspecified sites	Yes
Etoposide	Lymphoid leukaemia, NOS	Yes
Etoposide	Retinoblastoma	Yes
Fludarabine	Chronic lymphocytic leukaemia or small lymphocytic lymphoma	Yes
Fluorouracil	Malignant neoplasms of breast	Yes
Fluorouracil	Malignant neoplasm metastasis in large intestine	Yes
Fluorouracil	Malignant neoplasms of rectum	Yes
Fluorouracil	Malignant neoplasms of colon	Yes
Fluorouracil	Malignant neoplasms of nasopharynx	Yes
Gefitinib	Other specified malignant neoplasms of bronchus or lung	Yes
Gemcitabine	Other specified carcinomas of ovary	Yes
Gemcitabine	Other specified malignant neoplasms of bronchus or lung	Yes
Hydroxycarbamide	Chronic myeloid leukaemia, NOS	Yes
Hydrocortisone	Lymphoid leukaemia, NOS	Yes
Ifosfamide	Other specified malignant neoplasms of the ovary	Yes
Ifosfamide	Ewing sarcoma of bone and articular cartilage of unspecified sites	Yes

Medicine	Indication as per WHO-EML	Funded in Aotearoa
Ifosfamide	Germ cell tumour of testis	Yes
Ifosfamide	Osteosarcoma of bone and articular cartilage of unspecified sites	Yes
Ifosfamide	Rhabdomyosarcoma primary site	Yes
Imatinib	Gastrointestinal stromal tumour of unspecified gastrointestinal sites	Yes
Imatinib	Chronic myeloid leukaemia, NOS	Yes
Irinotecan	Malignant neoplasm metastasis in large intestine	Yes
Lenalidomide	Plasma cell myeloma	Yes
Leuprorelin	Malignant neoplasms of prostate	Yes (part charge applies) (The WHO recommends leuprorelin as an example of medicines from the gonadotropin releasing hormone analogue class of medicines. Goserelin, which also belongs to this class of medicines, is funded in Aotearoa without restriction.)
Leuprorelin	Malignant neoplasms of breast	Yes (part charge applies) (The WHO recommends leuprorelin as an example of medicines from the gonadotropin releasing hormone analogue class of medicines. Goserelin, which also belongs to this class of medicines, is funded in Aotearoa without restriction.)
Melphalan	Plasma cell myeloma	Yes
Mercaptopurine	Lymphoid leukaemia, NOS	Yes
Mercaptopurine	Acute myeloid leukaemia with recurrent genetic abnormalities	Yes
Methotrexate	Acute myeloid leukaemia with recurrent genetic abnormalities	Yes
Methotrexate	Lymphoid leukaemia, NOS	Yes
Methotrexate	Malignant neoplasms of breast	Yes
Methotrexate	Malignant trophoblastic neoplasms of placenta	Yes
Methotrexate	Osteosarcoma of bone and articular cartilage of unspecified sites	Yes
Methylprednisolone	Lymphoid leukaemia, NOS	Yes
Nivolumab	Melanoma of skin	Yes
Oxaliplatin	Malignant neoplasms of colon	Yes

Medicine	Indication as per WHO-EML	Funded in Aotearoa
Oxaliplatin	Malignant neoplasm metastasis in large intestine	Yes
Paclitaxel	Other specified malignant neoplasms of the ovary	Yes
Paclitaxel	Other specified malignant neoplasms of bronchus or lung	Yes
Paclitaxel	Kaposi sarcoma of unspecified primary site	Yes
Paclitaxel	Malignant neoplasms of nasopharynx	Yes
Paclitaxel	Other specified malignant neoplasms of breast	Yes
Paclitaxel	Other specified carcinomas of ovary	Yes
Paclitaxel	Malignant neoplasms of breast	Yes
Paclitaxel	Malignant neoplasms of cervix uteri	Yes
Pegaspargase	Lymphoid leukaemia, NOS	Yes
Pembrolizumab	Melanoma of skin	Yes
Prednisolone	Follicular lymphoma	No Prednisone is therapeutically equivalent and is funded in Aotearoa without restriction
Prednisolone	Chronic lymphocytic leukaemia or small lymphocytic lymphoma	No Prednisone is therapeutically equivalent and is funded in Aotearoa without restriction
Prednisolone	Diffuse large B-cell lymphomas	No Prednisone is therapeutically equivalent and is funded in Aotearoa without restriction
Prednisolone	Hodgkin lymphoma	No Prednisone is therapeutically equivalent and is funded in Aotearoa without restriction
Prednisolone	Lymphoid leukaemia, NOS	No Prednisone is therapeutically equivalent and is funded in Aotearoa without restriction
Prednisolone	Burkitt lymphoma, including Burkitt leukaemia	No Prednisone is therapeutically equivalent and is funded in Aotearoa without restriction

Medicine	Indication as per WHO-EML	Funded in Aotearoa
Prednisolone	Plasma cell myeloma	No Prednisone is therapeutically equivalent and is funded in Aotearoa without restriction
Procarbazine	Hodgkin lymphoma	Yes
Realgar-indigo naturalis formulation [oral arsenic]	Acute myeloid leukaemia with recurrent genetic abnormalities	No Arsenic trioxide injection is a therapeutic alternative to realgar-indigo naturalis and is funded in Aotearoa without restriction.
Rituximab	Follicular lymphoma	Yes
Rituximab	Chronic lymphocytic leukaemia or small lymphocytic lymphoma	Yes
Rituximab	Diffuse large B-cell lymphomas	Yes
Tamoxifen	Other specified malignant neoplasms of breast	Yes
Tamoxifen	Malignant neoplasms of breast	Yes
Thalidomide	Plasma cell myeloma	Yes
Trastuzumab	Carcinoma of breast, specialised type	Yes
Vinblastine	Hodgkin lymphoma	Yes
Vinblastine	Kaposi sarcoma of unspecified primary site	Yes
Vinblastine	Germ cell tumour of testis	Yes
Vinblastine	Other specified malignant neoplasms of the ovary	Yes
Vincristine	Kaposi sarcoma of other specified primary sites	Yes
Vincristine	Malignant trophoblastic neoplasms of placenta	Yes
Vincristine	Malignant neoplasms of kidney, except renal pelvis	Yes
Vincristine	Ewing sarcoma of bone and articular cartilage of unspecified sites	Yes
Vincristine	Follicular lymphoma	Yes
Vincristine	Lymphoid leukaemia, NOS	Yes
Vincristine	Rhabdomyosarcoma primary site	Yes
Vincristine	Diffuse large B-cell lymphomas	Yes
Vincristine	Retinoblastoma	Yes
Vincristine	Hodgkin lymphoma	Yes

Medicine	Indication as per WHO-EML	Funded in Aotearoa
Vincristine	Burkitt lymphoma, including Burkitt leukaemia	Yes
Vinorelbine	Other specified malignant neoplasms of bronchus or lung	Yes
Vinorelbine	Other specified malignant neoplasms of breast	Yes

* NOS = not otherwise specified.

Appendix 3: Results table from the comparison with the Australian Pharmaceutical Benefits Schedule (PBS) – medicines funded in both countries

This appendix provides results from the comparison of cancer medicines publicly funded in Aotearoa with those included in the Australian PBS list of pharmaceuticals, specifically for medicines funded in both jurisdictions (Table 3.1).

Table 3.1: Medicines funded in both Aotearoa and Australia (including for haematology indications)

Medicine	Funded indication†
Abiraterone	Prostate cancer
Alectinib	Lung cancer
Anastrozole**	Breast cancer
Arsenic trioxide**	Acute promyelocytic leukaemia***
Azacitidine	Acute myeloid leukaemia***
Azacitidine	Chronic myeloid leukaemia***
Azacitidine	Myelodysplastic syndrome***
Bendamustine	Indolent non-Hodgkin lymphoma***
Bendamustine	Mantle cell lymphoma***
Bicalutamide**	Prostate cancer
Bleomycin**	Germ cell cancer
Bleomycin**	Lymphoma
Bortezomib	Multiple myeloma***
Busulfan	No restriction on cancer type
Capecitabine	No restriction on cancer type
Carboplatin	No restriction on cancer type
Cetuximab	Head and neck cancer
Chlorambucil	No restriction on cancer type
Cisplatin	No restriction on cancer type
Cladribine**	Hairy cell leukaemia***
Cyclophosphamide	No restriction on cancer type
Cyproterone	No restriction on cancer type
Cytarabine	No restriction on cancer type

Medicine	Funded indication†
Dasatinib	Acute lymphocytic leukaemia***
Dasatinib	Chronic myeloid leukaemia***
Docetaxel	No restriction on cancer type
Doxorubicin	No restriction on cancer type
Epirubicin	No restriction on cancer type
Erlotinib	Lung cancer
Etoposide	No restriction on cancer type
Exemestane**	Breast cancer
Fludarabine	No restriction on cancer type
Fluorouracil	No restriction on cancer type
Flutamide**	Prostate cancer
Fulvestrant	Breast cancer (second line)
Gefitinib	Lung cancer
Gemcitabine	No restriction on cancer type
Goserelin**	Prostate cancer
Goserelin**	Breast cancer
Hydroxycarbamide [hydroxyurea]	No restriction on cancer type
Idarubicin**	Acute myeloid leukaemia***
Ifosfamide	No restriction on cancer type
Imatinib**	Acute lymphoblastic leukaemia***
Imatinib**	Chronic eosinophilic leukaemia
Imatinib**	Chronic myeloid leukaemia
Imatinib**	Dermatofibrosarcoma protuberans
Imatinib	Gastrointestinal stromal tumour
Imatinib**	Myelodysplastic syndrome
Irinotecan	No restriction on cancer type
Lapatinib	Breast cancer
Lenalidomide	Multiple myeloma (maintenance – post autologous stem cell transplant)***
Lenalidomide	Multiple myeloma (relapsed/refractory, after at least one line of treatment, with dexamethasone, transplant ineligible)***
Letrozole**	Breast cancer
Medroxyprogesterone**	Breast cancer
Medroxyprogesterone**	Endometrial cancer
Melphalan	No restriction on cancer type
Mercaptopurine	No restriction on cancer type
Methotrexate	No restriction on cancer type

Medicine	Funded indication†
Mitozantrone	No restriction on cancer type
Mycobacterium bovis (BCG) TICE strain	Urothelial (bladder) cancer
Nilotinib	Chronic myeloid leukaemia***
Nivolumab	Melanoma (unresectable)
Obinutuzumab	Chronic lymphocytic leukaemia***
Octreotide (long acting)	Neuroendocrine cancer (functional)
Olaparib	Ovarian cancer (second line)
Oxaliplatin	No restriction on cancer type
Paclitaxel	No restriction on cancer type
Palbociclib	Breast cancer
Pazopanib	Renal cell carcinoma
Pembrolizumab	Melanoma (unresectable)
Pemetrexed*	Mesothelioma
Pemetrexed*	Non-small cell lung cancer
Pertuzumab	Breast cancer
Rituximab	Acute lymphoblastic leukaemia***
Rituximab	B-cell lymphoma (induction/re-induction)***
Rituximab	B-cell lymphoma (maintenance)***
Rituximab	Chronic lymphocytic leukaemia***
Sunitinib	Renal cell carcinoma
Sunitinib	Gastrointestinal stromal tumour
Tamoxifen**	Breast cancer
Temozolomide*	Anaplastic astrocytoma
Temozolomide*	Ewing's sarcoma
Temozolomide*	Glioblastoma multiforme
Temozolomide*	Neuroendocrine cancer
Thalidomide	Multiple myeloma***
Thioguanine [tioguanine]	No restriction on cancer type
Trastuzumab	Breast cancer (early)
Trastuzumab	Breast cancer (advanced)
Trastuzumab emtansine	Breast cancer (advanced)
Venetoclax	Chronic lymphocytic leukaemia***
Vinblastine	No restriction on cancer type
Vincristine	No restriction on cancer type
Vinorelbine	No restriction on cancer type

† These are broad descriptions of indication and further restrictions may apply – please refer to the PBS and Pharmac schedules for more information.

* Funded without restriction in Australia. Indications from TGA-approved product information and eviQ.

** Funded without restriction in Aotearoa. Indications from PBS.

*** Haematology indications; some specified indications may be non-malignant haematological disorders.

Appendix 4: Results table from the comparison with the Australian Pharmaceutical Benefits Schedule (PBS) – medicines funded in Aotearoa but not Australia

This appendix provides results from the comparison of cancer medicines publicly funded in Aotearoa with those included in the Australian PBS list of pharmaceuticals, specifically for medicines funded in Aotearoa but not in Australia (Table 4.1).

Table 4.1: Medicines funded in Aotearoa but not in Australia*

Medicine	Indication per Pharmac's schedule**
Amsacrine	No restriction on cancer type
Anagrelide hydrochloride	No restriction on cancer type
Bendamustine	Chronic lymphocytic leukaemia
Bendamustine	Hodgkin lymphoma
Carmustine – injection	No restriction on cancer type
Dacarbazine	No restriction on cancer type
Dactinomycin	No restriction on cancer type
Daunorubicin	No restriction on cancer type
Lomustine^	No restriction on cancer type
Mitomycin C	No restriction on cancer type
Pegaspargase	Acute lymphoblastic leukaemia
Pentostatin	No restriction on cancer type
Procarbazine	No restriction on cancer type
Thiotepa	No restriction on cancer type
Zoledronic acid	Breast cancer (early, post-menopausal)

* In contrast to Aotearoa, medicines used by in-patients in public hospitals in Australia are not funded via the PBS. Instead, individual states have different public funding arrangements in place – either at a state-wide level or at different health districts or individual hospital levels. Therefore, some of these medicines may be publicly funded by mechanisms other than the PBS.

** Some of these medicines may only have haematological indications.

^ Lomustine will be discontinued by the supplier in Aotearoa and Australia in 2022.

Appendix 5: Results tables from the comparison with the Australian Pharmaceutical Benefits Schedule (PBS) – medicines funded in Australia but not in Aotearoa

This appendix provides results from the comparison of cancer medicines publicly funded in Aotearoa with those included in the Australian PBS list of pharmaceuticals, specifically for medicines funded in Australia but not in Aotearoa.

Tables 5.1–5.5 focus on the medicines funded in Australia but not in Aotearoa by ESMO-MCBS scores. Table 5.1 lists medicines that had an ESMO-MCBS score of A, indicating substantial clinical benefit in the curative setting as defined by ESMO. It provides details on how the gaps were ultimately categorised, informed by this score and by confirmation/checking with clinical advisors. It should be noted that there were no medicines and indications with an ESMO-MCBS score of B (also indicative of substantial clinical benefit in the curative setting).

Table 5.1: Medicines funded in Australia but not in Aotearoa with an ESMO-MCBS score of A

Medicine	Indication per PBS	Final gap categorisation
Dabrafenib	Melanoma (stage III, BRAF +ve, adjuvant to surgery) Used in combination with trametinib	Gap – substantial clinical benefit ESMO-MCBS score relevant to Aotearoa Both dabrafenib and trametinib would need to be funded for this indication for this gap to be filled. See Appendix 7, Table 7.18 for more information.
Nivolumab	Melanoma (stage III, adjuvant to surgery)	Gap – substantial clinical benefit ESMO-MCBS score is based on a comparator that isn't funded in Aotearoa – ipilimumab. Nivolumab is likely to be even more effective when compared to the current standard of care in Aotearoa – watch and wait. Nivolumab is funded in Aotearoa but not for this indication. Pembrolizumab is an alternative option to fill this gap. See Appendix 7, Table 7.17 for more information.

Medicine	Indication per PBS	Final gap categorisation
Pembrolizumab	Melanoma (stage III or IV, adjuvant to surgery)	Gap – substantial clinical benefit ESMO-MCBS score relevant to Aotearoa Pembrolizumab is funded in Aotearoa but not for this indication. Nivolumab is an alternative option to fill this gap. See Appendix 7, Table 7.17 for more information.
Trametinib	Melanoma (stage III, BRAF +ve, adjuvant to surgery) Used in combination with dabrafenib	Gap – substantial clinical benefit ESMO-MCBS score relevant to Aotearoa Both trametinib and dabrafenib would need to be funded for this indication for this gap to be filled. See Appendix 7, Table 7.18 for more information.

Tables 5.2 and 5.3 list medicines funded in Australia but not Aotearoa that had an ESMO-MCBS score of 5 and 4 respectively, indicating substantial clinical benefit in the non-curative setting as defined by ESMO. As before, the tables also include information on how the gaps were categorised.

Table 5.2: Medicines funded in Australia and not in Aotearoa – ESMO-MCBS score of 5

Medicine	Indication per PBS	Final gap categorisation
Atezolizumab	Liver cancer (hepatocellular carcinoma (HCC), advanced (unresectable), Barcelona Clinic Liver Cancer stage B or C, first-line) Used in combination with bevacizumab	Gap – substantial clinical benefit ESMO-MCBS score is based on a comparator that isn't funded in Aotearoa – sorafenib. This regimen is likely to be even more effective when compared to the current standard of care in Aotearoa, which is best supportive care. Both atezolizumab and bevacizumab would need to be funded for this indication for this gap to be filled. See Appendix 7, Table 7.7 for more information.
Atezolizumab	Lung cancer (non-small cell lung cancer (NSCLC), locally advanced or metastatic, second-line)	Gap – substantial clinical benefit ESMO-MCBS score relevant to Aotearoa Nivolumab is an alternative option to fill this gap. If an immune checkpoint inhibitor were funded in the first-line setting, this gap would be superseded. See Appendix 7, Table 7.2 for more information.

Medicine	Indication per PBS	Final gap categorisation
Bevacizumab*	Liver cancer (hepatocellular carcinoma (HCC), advanced (unresectable), Barcelona Clinic Liver Cancer stage B or C, first-line) Used in combination with atezolizumab	Gap – substantial clinical benefit ESMO-MCBS score is based on a comparator that isn't funded in Aotearoa – sorafenib. This regimen is likely to be even more effective when compared to the current standard of care in Aotearoa – best supportive care. Both bevacizumab and atezolizumab would need to be funded for this indication for this gap to be filled. See Appendix 7, Table 7.7 for more information.
Dabrafenib	Melanoma (stage III or IV, BRAF +ve, unresectable) Used in combination with trametinib	Gap – substantial clinical benefit ESMO-MCBS score is based on a comparator that isn't funded in Aotearoa – vemurafenib. Clinical advice indicated this regimen is likely to score at least 4 for this specific patient group when compared with the current standard of care in Aotearoa – pembrolizumab or nivolumab. Both dabrafenib and trametinib would need to be funded for this indication for this gap to be filled. Other BRAF-MEK combinations are alternative options to fill this gap. See Appendix 7, Table 7.20 for more information.
Nivolumab	Head and neck cancer (head and neck squamous cell carcinoma (HNSCC), locally recurrent or metastatic, second-line)	Gap – substantial clinical benefit ESMO-MCBS score relevant to Aotearoa Nivolumab is funded in Aotearoa but not for this indication. See Appendix 7, Table 7.16 for more information.
Nivolumab	Lung cancer (non-small cell lung cancer (NSCLC), locally advanced or metastatic, 2Lsecond-line)	Gap – substantial clinical benefit ESMO-MCBS score relevant to Aotearoa Nivolumab is funded in Aotearoa but not for this indication. Atezolizumab is an alternative option to fill this gap. If an immune checkpoint inhibitor were funded in the first-line setting, this gap would be superseded. See Appendix 7, Table 7.2 for more information.

Medicine	Indication per PBS	Final gap categorisation
Nivolumab	Kidney cancer (renal cell carcinoma (RCC) clear cell variant (kidney cancer, stage IV, 2Lsecond-line)	Gap – substantial clinical benefit ESMO-MCBS score is based on a comparator that isn't funded in Aotearoa – everolimus. This regimen is likely to be even more effective when compared to the current standard of care in Aotearoa, which is best supportive care. Nivolumab is funded in Aotearoa but not for this indication. See Appendix 7, Table 7.11 for more information.
Pembrolizumab	Lung cancer (non-small cell lung cancer (NSCLC), stage IV, first-line) ^ Used with or without chemotherapy^	Gap – substantial clinical benefit ESMO-MCBS score relevant to Aotearoa Pembrolizumab is funded in Aotearoa but not for this indication. Other immune checkpoint inhibitor options exist as alternative options to fill this gap. See Appendix 7, Table 7.1 for more information.
Trametinib	Melanoma (stage III or IV, unresectable, BRAF +ve) Used with dabrafenib	Gap – substantial clinical benefit ESMO-MCBS score is based on a comparator that isn't funded in Aotearoa – vemurafenib. This regimen is considered likely to score at least 4 for this specific patient group when compared with the current standard of care in Aotearoa – pembrolizumab or nivolumab. Both trametinib and dabrafenib would need to be funded for this indication for this gap to be filled. Other BRAF-MEK combinations are alternative options to fill this gap. See Appendix 7, Table 7.20 for more information.

* Bevacizumab is funded without restriction in Australia, but the atezolizumab funding criteria for this indication require combination use with bevacizumab.

^ In clinical trials of immunotherapies such as pembrolizumab, the regimens used and clinical efficacy differ based on PD-L1 status of the lung cancer. Pharmac has active funding applications both with and without regard to PD-L1 status. In Australia, immunotherapies are funded without requirements regarding PD-L1 status, and pembrolizumab may be used with or without concomitant chemotherapy. Therefore both 'PD-L1 high' and 'regardless of PD-L1 status' have been considered together as one group for the purpose of this analysis. For this gap to be filled in its entirety, the Pharmac funding criteria in Aotearoa would need to mirror those in Australia.

Table 5.3: Medicines funded in Australia and not in Aotearoa – ESMO-MCBS score of 4

Medicine	Indication per PBS	Gap categorisation
Afatinib	Lung cancer (non-small cell lung cancer (NSCLC), stage IIIb or IV, EGFR+ve, first-line)	Gap – **not** substantial clinical benefit The ESMO-MCBS score is based on a superseded comparator – chemotherapy. The relevant comparator for Aotearoa is gefitinib or erlotinib. Clinical advice and the WHO-EML indicate that afatinib is unlikely to score 4 or 5 against either of these comparators for this indication.
Axitinib	Kidney cancer (renal cell carcinoma (RCC), clear cell variant, stage IV, second-line)	Gap – substantial clinical benefit The ESMO-MCBS score is based on a comparator that isn't funded in Aotearoa – sorafenib. This regimen is likely to be even more effective when compared with the current standard of care in Aotearoa, which is best supportive care. See Appendix 7, Table 7.12 for more information.
Bevacizumab*	Ovarian cancer (epithelial ovarian, fallopian tube or primary peritoneal cancer, second-line) Used in combination with chemotherapy	Gap – substantial clinical benefit ESMO-MCBS score relevant to Aotearoa Bevacizumab is funded in Aotearoa but not for this indication. Chemotherapy used with bevacizumab for this indication is funded in Aotearoa. See Appendix 7, Table 7.15 for more information.
Binimetinib	Melanoma (stage III or IV, unresectable, BRAF +ve) Used in combination with encorafenib	Gap – substantial clinical benefit The ESMO-MCBS score is based on a comparator that isn't funded in Aotearoa – vemurafenib. Clinical advice indicated this regimen is likely to score at least 4 for this specific patient group when compared with the current standard of care in Aotearoa – pembrolizumab or nivolumab. Both binimetinib and encorafenib would need to be funded for this indication for this gap to be filled. Other BRAF-MEK combinations are alternative options to fill this gap. See Appendix 7, Table 7.20 for more information.
Ceritinib	Lung cancer (non-small cell lung cancer (NSCLC), stage IIIb or IV, ALK+ve, first-line)	Gap – **not** substantial clinical benefit The ESMO-MCBS score is based on a superseded comparator – chemotherapy. Standard care in Aotearoa is alectinib. Clinical advice indicated that ceritinib is unlikely to score 4 or 5 against this comparator for this indication.

Medicine	Indication per PBS	Gap categorisation
Cetuximab	Bowel cancer (colorectal cancer (CRC), metastatic, RAS wild-type, first-line) Used in combination with chemotherapy	Gap – substantial clinical benefit ESMO-MCBS score relevant to Aotearoa Cetuximab is funded in Aotearoa but not for this indication. Chemotherapy used with cetuximab for this indication is funded in Aotearoa. Panitumumab is an alternative option to fill this gap. See Appendix 7, Table 7.8 for more information.
Cetuximab	Bowel cancer (colorectal cancer (CRC), metastatic, RAS wild-type, second-line) Used with or without chemotherapy	Gap – substantial clinical benefit ESMO-MCBS score relevant to Aotearoa Cetuximab is funded in Aotearoa but not for this indication. Chemotherapy used with cetuximab for this indication is funded in Aotearoa. See Appendix 7, Table 7.9 for more information.
Cobimetinib	Melanoma (stage III or IV, unresectable, BRAF +ve) Used in combination with vemurafenib	Gap – substantial clinical benefit The ESMO-MCBS score is based on a comparator that isn't funded in Aotearoa – vemurafenib. Clinical advice indicated that this regimen is likely to score at least 4 for this specific patient group when compared with the current standard of care in Aotearoa – pembrolizumab or nivolumab. Both cobimetinib and vemurafenib would need to be funded for this indication for this gap to be filled. Other BRAF-MEK combinations are alternative options to fill this gap. See Appendix 7, Table 7.20 for more information.
Crizotinib	Lung cancer (non-small cell lung cancer (NSCLC), stage IIIb or IV, ALK+ve)	Gap – **not** substantial clinical benefit The ESMO-MCBS score is based on a superseded comparator– chemotherapy. Standard care in Aotearoa is alectinib. Clinical advice indicated that crizotinib is unlikely to score 4 or 5 against this comparator for this indication.
Durvalumab	Lung cancer (non-small cell lung cancer (NSCLC), stage III, consolidation after chemoradiotherapy)	Gap– substantial clinical benefit ESMO-MCBS score relevant to Aotearoa Note: After this analysis had been completed, Pharmac approved funding of durvalumab for this indication, and therefore this gap will be filled from August 2022. See Appendix 7, Table 7.3 for more information.

Medicine	Indication per PBS	Gap categorisation
Encorafenib	Melanoma (stage III or IV, unresectable, BRAF +ve) Used in combination with binimetinib	Gap – substantial clinical benefit The ESMO-MCBS score is based on a comparator that isn't funded in Aotearoa – vemurafenib. Clinical advice indicated this regimen is likely to score at least 4 for this specific patient group when compared with the current standard of care in Aotearoa – pembrolizumab or nivolumab. Both encorafenib and binimetinib would need to be funded for this indication for this gap to be filled. Other BRAF-MEK combinations are alternative options to fill this gap. See Appendix 7, Table 7.20 for more information.
Enzalutamide	Prostate cancer (metastatic, castration resistant, second-line)	Gap – **not** substantial clinical benefit The ESMO-MCBS score is against a superseded comparator– placebo. Standard care in Aotearoa is abiraterone. Clinical advice indicated that enzalutamide is unlikely to score 4 or 5 against this comparator for this indication.
Ipilimumab	Lung cancer (non-small cell lung cancer (NSCLC), stage IV, first-line) Used in combination with nivolumab and chemotherapy	Gap – substantial clinical benefit ESMO-MCBS score relevant to Aotearoa Requires funding of both ipilimumab and nivolumab for this indication for this gap to be filled. Chemotherapy used in this regimen for this indication is funded in Aotearoa. Other immune checkpoint inhibitor options exist as alternative options to fill this gap. See Appendix 7, Table 7.1 for more information.
Ipilimumab	Melanoma (stage III or IV, unresectable, induction)	Gap –uncategorised (unable to determine relevant ESMO-MCBS score) The ESMO-MCBS score is against a superseded comparator – chemotherapy. Standard care in Aotearoa is pembrolizumab or nivolumab. Unable to identify relevant data to inform a score against one of these comparators.

Medicine	Indication per PBS	Gap categorisation
Ipilimumab	Melanoma (stage III or IV, unresectable, first line induction) Used in combination with nivolumab	Gap – substantial clinical benefit The ESMO-MCBS score for the nivolumab/ipilimumab combination is against a comparator that is not funded in Aotearoa – ipilimumab. Standard care in Aotearoa is pembrolizumab or nivolumab. Clinical advice indicated that ipilimumab added in to nivolumab for induction in high-risk patients would likely score at least 4 when compared with nivolumab alone. Funding of ipilimumab in addition to nivolumab for this indication would be needed to fill this gap. See Appendix 7, Table 7.19 for more information.
Ipilimumab	Kidney cancer (renal cell carcinoma (RCC), clear cell variant, stage IV, intermediate/poor risk, first-line) Used in combination with nivolumab	Gap – substantial clinical benefit ESMO-MCBS score relevant to Aotearoa Requires funding of both ipilimumab and nivolumab for this indication for this gap to be filled. See Appendix 7, Table 7.10 for more information.
Nivolumab	Lung cancer (non-small cell lung cancer (NSCLC), stage IV, first-line) Used in combination with ipilimumab and chemotherapy	Gap – substantial clinical benefit ESMO-MCBS score relevant to Aotearoa Nivolumab is funded in Aotearoa but not for this indication. Requires funding of both nivolumab and ipilimumab for this indication for this gap to be filled. Chemotherapy used in this regimen for this indication is funded in Aotearoa. Other immune checkpoint inhibitor options exist as alternative options to fill this gap. See Appendix 7, Table 7.1 for more information.
Nivolumab	Melanoma (stage III or IV, unresectable, induction) Used in combination with ipilimumab	Gap – substantial clinical benefit The ESMO-MCBS score for nivolumab/ipilimumab combination is against a comparator that is not funded in Aotearoa – ipilimumab. Standard care in Aotearoa is pembrolizumab or nivolumab. Clinical advice indicated that ipilimumab added in to nivolumab for induction in high-risk patients would likely score at least 4 when compared to nivolumab alone. Nivolumab is funded in Aotearoa for stage III or IV unresectable melanoma. Funding of ipilimumab in addition to nivolumab for this indication would be needed to fill this gap. See Appendix 7, Table 7.19 for more information.

Medicine	Indication per PBS	Gap categorisation
Nivolumab	Kidney cancer (renal cell carcinoma (RCC), clear cell variant, stage IV, intermediate/poor risk, first-line) Used in combination with ipilimumab	Gap – substantial clinical benefit ESMO-MCBS score relevant to Aotearoa Nivolumab is funded in Aotearoa but not for this indication. Requires funding of both ipilimumab and nivolumab for this indication for this gap to be filled. See Appendix 7, Table 7.10 for more information.
Olaparib	Ovarian cancer (Epithelial ovarian, fallopian tube or primary peritoneal cancer, BRCA +ve [germline and/or somatic], first-line maintenance)	Gap – substantial clinical benefit ESMO-MCBS score relevant to Aotearoa Olaparib is funded in Aotearoa but not for this indication. Note: After this analysis was completed, Pharmac approved funding of olaparib for a large part of this indication (germline but not somatic BRCA mutation), and therefore this gap will be partially filled from August 2022. See Appendix 7, Table 7.14 for more information.
Osimertinib	Lung cancer (non-small cell lung cancer (NSCLC), stage IIIb or IV, EGFR+ve, first-line)	Gap – substantial clinical benefit ESMO-MCBS score relevant to Aotearoa See Appendix 7, Table 7.4 for more information.
Osimertinib	Lung cancer (non-small cell lung cancer (NSCLC), stage IIIb or IV, EGFR+ve T790M mutation, second-line)	Gap – substantial clinical benefit ESMO-MCBS score relevant to Aotearoa If osimertinib were funded in the first-line setting, this gap would be superseded. See Appendix 7, Table 7.5 for more information.
Panitumumab	Bowel cancer (colorectal cancer (CRC), metastatic, RAS wild-type, first-line) Used in combination with chemotherapy	Gap – substantial clinical benefit ESMO-MCBS score relevant to Aotearoa Chemotherapy used in this regimen for this indication is funded in Aotearoa. Cetuximab is an alternative option to fill this gap. See Appendix 7, Table 7.8 for more information.
Pembrolizumab	Bladder cancer (urothelial cancer, locally advanced or metastatic, second-line)	Gap – substantial clinical benefit ESMO-MCBS score relevant to Aotearoa Pembrolizumab is funded in Aotearoa but not for this indication. See Appendix 7, Table 7.13 for more information.

Medicine	Indication per PBS	Gap categorisation
Ribociclib	Breast cancer (locally advanced or metastatic, unresectable, HR+ve, HER-2 +ve, first-line) Used in combination with endocrine therapy	Gap – **not** substantial clinical benefit The ESMO-MCBS score is based on a superseded comparator – placebo. Standard care in Aotearoa is palbociclib (used with endocrine therapy). Clinical advice indicated that ribociclib is unlikely to score 4 or 5 against this comparator for this indication.
Vemurafenib	Melanoma (stage III or IV, unresectable, BRAF +ve) Used in combination with cobimetinib	Gap – substantial clinical benefit The ESMO-MCBS score is based on a comparator that isn't funded in Aotearoa – vemurafenib. This regimen is considered likely to score at least 4 for this specific patient group when compared with the current standard of care in Aotearoa – pembrolizumab or nivolumab. Both vemurafenib and cobimetinib would need to be funded for this indication for this gap to be filled. Other BRAF-MEK combinations are alternative options to fill this gap. See Appendix 7, Table 7.20 for more information.

* Funded without restriction in Australia. Indications from TGA-approved product information and eviQ.

Tables 5.4 and 5.5 show medicines funded in Australia but not in Aotearoa with an ESMO-MCBS score of 3 and 2 respectively, which is below the threshold of substantial clinical benefit as defined by ESMO. These tables provide information on how gaps were categorised, including instances where the scores were upgraded for the Aotearoa context.

Table 5.4: Medicines funded in Australia and not in Aotearoa – ESMO-MCBS score of 3

Medicine	Indication as per PBS	Final gap categorisation
Abemaciclib	Breast cancer (locally advanced or metastatic, HR+ve, HER-2 -ve, unresectable) Used in combination with endocrine therapy	Gap – not substantial clinical benefit ESMO-MCBS comparator is placebo. No clinical advice sought.
Atezolizumab	Lung cancer (small cell lung cancer (SCLC), extensive disease, first-line) Used in combination with chemotherapy	Gap – not substantial clinical benefit ESMO-MCBS comparator is placebo. No clinical advice sought.
Atezolizumab	Lung cancer (non-small cell lung cancer (NSCLC), stage IV, first-line) Used in combination with bevacizumab and chemotherapy	Gap – **substantial** clinical benefit The ESMO-MCBS score is based on a comparator that is not funded for this indication in Aotearoa – bevacizumab (used with chemotherapy). Clinical advice indicated this regimen is considered likely to score at least 4 when compared to the current standard of care in Aotearoa – chemotherapy. Other immune checkpoint inhibitor options exist as alternative options to fill this gap. See Appendix 7, Table 7.1 for more information.
Avelumab	Merkel cell carcinoma (stage IV)	Gap – not substantial clinical benefit The ESMO-MCBS score is based on a single-arm study – no comparator. No clinical advice sought.
Bevacizumab*	Cervical cancer (persistent, recurrent or metastatic) Used in combination with chemotherapy	Gap – not substantial clinical benefit The ESMO-MCBS comparator is chemotherapy. Funded in Aotearoa without restriction. No clinical advice sought.
Bevacizumab*	Colorectal Bowel cancer (colorectal cancer, metastatic) Used in combination with chemotherapy	Gap – not substantial clinical benefit The ESMO-MCBS comparator is chemotherapy. Funded in Aotearoa without restriction. No clinical advice sought.
Bevacizumab*	Kidney cancer (renal cell carcinoma (RCC), locally advanced or metastatic) Used in combination with interferon	Gap – not substantial clinical benefit The ESMO-MCBS comparator is interferon. Interferon alpha-2b is funded in Aotearoa without restriction. No clinical advice sought.

Medicine	Indication as per PBS	Final gap categorisation
Bevacizumab*	Lung cancer (non-small cell lung cancer (NSCLC), stage IV, first-line) Used in combination with atezolizumab and chemotherapy	Gap – **substantial** clinical benefit The ESMO-MCBS score is based on a comparator that is not funded for this indication in Aotearoa – bevacizumab (used with chemotherapy). Clinical advice indicated this regimen is considered likely to score at least 4 when compared with the current standard of care in Aotearoa – chemotherapy. Other immune checkpoint inhibitor options exist as alternative options to fill this gap. See Appendix 7, Table 7.1 for more information.
Brigatinib	Lung cancer (non-small cell lung cancer (NSCLC), stage IIb or IV, ALK +ve)	Gap – not substantial clinical benefit The ESMO-MCBS score is based on a single-arm study – no comparator. No clinical advice sought.
Cabazitaxel	Prostate cancer (metastatic, castration-resistant, second-line) Used in combination with prednisolone	Gap – not substantial clinical benefit The ESMO-MCBS comparator is abiraterone or enzalutamide. Abiraterone is funded in Aotearoa for this indication. No clinical advice sought.
Cabozantinib	Kidney cancer (renal cell carcinoma (RCC), clear cell variant, stage IV, intermediate-poor risk, first-line)	Gap – not substantial clinical benefit The ESMO-MCBS comparator is sunitinib – funded in Aotearoa for this indication. No clinical advice sought.
Cabozantinib	Kidney cancer (renal cell carcinoma (RCC), clear cell variant, stage IV, intermediate-poor risk, second-line)	Gap –uncategorised (unable to determine relevant ESMO-MCBS score) The ESMO-MCBS comparator is everolimus – not funded in Aotearoa for this indication. Standard care is best supportive care. Clinical advice was inconclusive. Unable to identify relevant data to inform whether this score should be upgraded for the Aotearoa clinical context.
Crizotinib	Lung cancer (non-small cell lung cancer (NSCLC), stage IIIb or IV, ROS-1 +ve)	Gap – not substantial clinical benefit The ESMO-MCBS score is based on a single-arm study – no comparator. No clinical advice sought.
Entrectinib	Lung cancer (non-small cell lung cancer (NSCLC), stage IIIb or IV, ROS-1 +ve)	Gap – not substantial clinical benefit The ESMO-MCBS score is based on a single-arm study – no comparator. No clinical advice sought.
Eribulin	Liposarcoma (metastatic or unresectable, second-line)	Gap – not substantial clinical benefit The ESMO-MCBS comparator is dacarbazine, which is funded without restriction in Aotearoa. No clinical advice sought.

Medicine	Indication as per PBS	Final gap categorisation
Everolimus	Neuroendocrine cancer (metastatic or unresectable, symptomatic or progressive disease)	Gap – not substantial clinical benefit The ESMO-MCBS comparator is placebo. No clinical advice sought.
Everolimus	Kidney cancer (renal cell carcinoma (RCC), clear cell variant, stage IV)	Gap – not substantial clinical benefit The ESMO-MCBS comparator is placebo. No clinical advice sought.
Ipilimumab	Lung cancer (mesothelioma, unresectable) Used in combination with nivolumab	Gap – not substantial clinical benefit The ESMO-MCBS comparator is chemotherapy, including pemetrexed – funded in Aotearoa for this indication. No clinical advice sought.
Lanreotide	Neuroendocrine cancer (gastroenteropancreatic neuroendocrine tumour (GEP-NET), non-functional, unresectable locally advanced or metastatic)	Gap – not substantial clinical benefit The ESMO-MCBS comparator is placebo. No clinical advice sought.
Lenvatinib	Thyroid cancer (locally advanced or metastatic, unresectable, refractory to radioactive iodine)	Gap – not substantial clinical benefit The ESMO-MCBS comparator is placebo. No clinical advice sought.
Lorlatinib	Lung cancer (non-small cell lung cancer (NSCLC), stage IV, ALK +ve, second-line)	Gap – not substantial clinical benefit The ESMO-MCBS score is based on a single-arm study – no comparator. No clinical advice sought.
Nivolumab	Lung cancer (mesothelioma, unresectable) Used in combination with ipilimumab	Gap – not substantial clinical benefit The ESMO-MCBS comparator is chemotherapy, including pemetrexed – funded in Aotearoa for this indication. No clinical advice sought.
Panitumumab	Bowel cancer (colorectal cancer (CRC), metastatic, RAS-wild type, second-line) Used with or without chemotherapy	Gap – not substantial clinical benefit The ESMO-MCBS comparator is chemotherapy. Funded in Aotearoa without restriction. No clinical advice sought.
Pazopanib	Soft tissue sarcoma (locally advanced or metastatic, unresectable, second-line)	Gap – not substantial clinical benefit The ESMO-MCBS comparator is placebo. No clinical advice sought.
Sorafenib	Kidney cancer (renal cell carcinoma (RCC), clear cell variant, stage IV, second-line)	Gap – not substantial clinical benefit The ESMO-MCBS comparator is placebo. No clinical advice sought.
Sunitinib	Neuroendocrine cancer (pancreatic neuroendocrine tumour (PNET), metastatic or unresectable, symptomatic or disease progression)	Gap – not substantial clinical benefit The ESMO-MCBS comparator is placebo. No clinical advice sought.

Medicine	Indication as per PBS	Final gap categorisation
Trastuzumab	Stomach cancer (gastric or gastro-oesophageal junction cancer, stage IV, (HER 2 +ve IHC 2+, stage IV, first-line) Used in combination with chemotherapy.	Gap – uncategorised (unable to determine relevant ESMO-MCBS score) The ESMO-MCBS comparator is chemotherapy, which is funded in Aotearoa without restriction. However, the patient group included in the trial was not limited to IHC 2+. Unable to score this sub-group according to ESMO-MCBS methodology.
Trifluridine + tipiracil	Gastro-oesophageal cancer	Gap – not substantial clinical benefit The ESMO-MCBS comparator is placebo. No clinical advice sought.

* Funded without restriction in Australia. Indications from TGA-approved product information and eviQ.

Table 5.5: Medicines funded in Australia and not in Aotearoa – ESMO-MCBS score of 2

Medicine	Indication as per PBS	Final gap categorisation
Bevacizumab*	Breast cancer (locally recurrent or metastatic, first-line) Used with chemotherapy	Gap – not substantial clinical benefit The ESMO-MCBS comparator is chemotherapy, no clinical advice sought.
Bevacizumab*	Lung cancer (non-small cell lung cancer (NSCLC), locally advanced or metastatic, first-line) Used with chemotherapy	Gap – not substantial clinical benefit The ESMO-MCBS comparator is chemotherapy, no clinical advice sought.
Eribulin	Breast cancer (locally advanced or metastatic, third-line)	Gap – not substantial clinical benefit The ESMO-MCBS comparator is 'treatment of physician's choice', no clinical advice sought.
Everolimus	Breast cancer (stage IV, HR+, HER-2 -ve, endocrine resistant) Used with exemestane	Gap – not substantial clinical benefit The ESMO-MCBS comparator is placebo. No clinical advice sought.
Fulvestrant	Breast cancer (locally advanced or metastatic, HR+, HER-2-, unresectable, first-line)	Gap – not substantial clinical benefit The ESMO-MCBS comparator is anastrozole (funded in Aotearoa without restriction), no clinical advice sought.
Nab-paclitaxel	Pancreatic cancer (stage IV, first-line) Used with gemcitabine	Gap – not substantial clinical benefit The ESMO-MCBS comparator is gemcitabine (funded in Aotearoa without restriction), no clinical advice sought.
Trifluridine + tipiracil	Colorectal cancer (metastatic, later-line)	Gap – not substantial clinical benefit The ESMO-MCBS comparator is placebo, no clinical advice sought.

* Funded without restriction in Australia. Indications from TGA-approved product information and eviQ.

Table 5.6 shows medicines funded in Australia but not in Aotearoa where there was no ESMO-MCBS score available. This table provides information on how gaps were handled after checking/confirmation with clinical advisors, including input on a likely score for the Aotearoa context.

Table 5.6: Medicines funded in Australia and not in Aotearoa – ESMO-MCBS score not available for the funded indication

Medicine	Indication as per PBS	Final gap category
Bevacizumab*	Glioma (stage IV, relapsed or refractory, post standard care including chemotherapy)	Gap – not substantial clinical benefit Clinical advice indicated the relevant comparator would be best supportive care. Unlikely to score 4 or 5 against this comparator for this indication.
Carmustine – implant	Glioblastoma multiforme (suspected or confirmed at time of initial surgery)	Gap – not substantial clinical benefit Clinical advice indicated the relevant comparator would be carmustine injection. Unlikely to score 4 or 5 against this comparator for this indication.
Degarelix	Prostate cancer (locally advanced or metastatic)	Gap – not substantial clinical benefit Clinical advice indicated the relevant comparator would be goserelin. Unlikely to score 4 or 5 against this comparator for this indication.
Doxorubicin – pegylated liposomal	Breast cancer (metastatic, second-line)	Gap – not substantial clinical benefit Clinical advice indicated the relevant comparator would be standard doxorubicin. Unlikely to score 4 or 5 against this comparator for this indication.
Doxorubicin – pegylated liposomal	Kaposi sarcoma (AIDS-related, extensive mucocutaneous involvement)	Gap –uncategorised (unable to determine relevant ESMO-MCBS score) Clinical advice indicated the relevant comparator would be standard doxorubicin. Unclear whether doxorubicin – pegylated liposomal would score 4 or 5 against this comparator for this indication.
Doxorubicin – pegylated liposomal	Ovarian cancer (epithelial, advanced, second-line)	Gap – not substantial clinical benefit Clinical advice indicated the relevant comparator would be standard doxorubicin. Unlikely to score 4 or 5 against this comparator for this indication.
Fotemustine	Melanoma (metastatic)	Gap – not substantial clinical benefit Clinical advice indicated the relevant comparator would be pembrolizumab or nivolumab. Unlikely to score 4 or 5 against either of these comparators for this indication.

Medicine	Indication as per PBS	Final gap category
Lanreotide	Neuroendocrine cancer (functional carcinoid)	Gap – not substantial clinical benefit Clinical advice indicated the relevant comparator would be octreotide. Unlikely to score 4 or 5 against this comparator for this indication.
Lenvatinib	Liver cancer (hepatocellular carcinoma, advanced Barcelona Clinic Liver Cancer stage B or C, unresectable, not-suitable for TACE, first-line)	Gap – not substantial clinical benefit Clinical advice indicated the relevant comparator would be best supportive care. Based on a review of clinical evidence compared with sorafenib then extrapolated to sorafenib compared with best supportive care, lenvatinib is considered unlikely to score 4 or 5 against best supportive care for this indication.
Leuprorelin	Prostate cancer (locally advanced or metastatic)	Gap – not substantial clinical benefit Clinical advice indicated the relevant comparator would be goserelin. Unlikely to score 4 or 5 against this comparator for this indication.
Nab-paclitaxel	Breast cancer (metastatic)	Gap – not substantial clinical benefit Clinical advice indicated the relevant comparator would be standard paclitaxel. Unlikely to score 4 or 5 against this comparator for this indication.
Nab-paclitaxel	Breast cancer (HER-2 +ve)	Gap – not substantial clinical benefit Clinical advice indicated the relevant comparator would be standard paclitaxel. Unlikely to score 4 or 5 against this comparator for this indication.
Nilutamide	Prostate cancer (locally advanced or metastatic) Used with GnRH analogue or surgical orchidectomy	Gap – not substantial clinical benefit Clinical advice indicated the relevant comparator would be abiraterone. Unlikely to score 4 or 5 against this comparator for this indication.
Octreotide long-acting	Neuroendocrine cancer (non-functional gastroenteropancreatic neuroendocrine tumour (GEP-NET), unresectable locally advanced or metastatic)	Gap – not substantial clinical benefit Clinical advice indicated the relevant comparator would be best supportive care. Based on a review of clinical evidence compared with placebo, octreotide is considered unlikely to score 4 or 5 against best supportive care for this indication.
Raltitrexed	Colorectal cancer (advanced)	Gap – not substantial clinical benefit Clinical advice indicated the relevant comparator would be 5-fluorouracil (5-FU) or best supportive care (for those who are 5-FU intolerant). Unlikely to score 4 or 5 against 5-FU and clinical evidence unlikely to support a score of 4 or 5 against best supportive care for this indication.

Medicine	Indication as per PBS	Final gap category
Sonidegib	Skin cancer (basal cell carcinoma (BCC), locally advanced or metastatic, unresectable, 1st first-line)	Gap – not substantial clinical benefit Clinical advice indicated the relevant comparator would be best supportive care. Based on clinical assessment by eviQ (Cancer Institute NSW 2021a); unlikely to score ESMO-MCBS 4 or 5 when compared with best supportive care.
Sorafenib	Liver cancer (hepatocellular carcinoma (HCC), advanced Barcelona Clinic Liver Cancer stage B or C, first-line)	Gap – not substantial clinical benefit Clinical advice indicated the relevant comparator would be best supportive care. Unlikely to score 4 or 5 against this comparator for this indication.
Temozolomide*	Melanoma (metastatic)	Gap – not substantial clinical benefit Clinical advice indicated the comparator would be pembrolizumab or nivolumab. Unlikely to score 4 or 5 against either of these comparators for this indication.
Topotecan*	No restriction on cancer type – likely multiple indications	Gap – not substantial clinical benefit Based on clinical advice; unlikely to score ESMO-MCBS 4 or 5 against relevant comparators for indications of interest.
Trastuzumab emtansine	Breast cancer (early-stage, HER-2 +ve, adjuvant to neo-adjuvant trastuzumab with chemotherapy and surgery)	Gap – **substantial** clinical benefit Clinical advice indicated the comparator would be trastuzumab. Based on a review of clinical evidence, trastuzumab emtansine is considered likely to score at least B when compared with trastuzumab for this indication. See Appendix 7, Table 7.6 for further detail.
Triptorelin	Prostate cancer (locally advanced or metastatic)	Gap – not substantial clinical benefit Clinical advice indicated the relevant comparator would be goserelin. Unlikely to score 4 or 5 against this comparator for this indication.
Vinorelbine – oral	Breast cancer (advanced, later-line)	Gap – not substantial clinical benefit Clinical advice indicated the relevant comparator would be IV vinorelbine. Unlikely to score 4 or 5 against this comparator for this indication.
Vinorelbine – oral	Lung cancer (non-small cell lung cancer (NSCLC), locally advanced or metastatic)	Gap – not substantial clinical benefit Clinical advice indicated the relevant comparator would be IV vinorelbine. Unlikely to score 4 or 5 against this comparator for this indication.

Medicine	Indication as per PBS	Final gap category
Vismodegib	Skin cancer (basal cell carcinoma (BCC), locally advanced or metastatic, unresectable, first-line)	Gap – not substantial clinical benefit Clinical advice indicated the comparator would be best supportive care. Based on a clinical assessment by eviQ (Cancer Institute NSW 2021b); unlikely to score ESMO-MCBS 4 or 5 when compared with best supportive care.

* Funded without restriction in Australia. Indications from TGA-approved product information and eviQ.

Finally, Table 5.7 lists cancer medicines for blood cancers that were funded in Australia but not Aotearoa. While the ESMO-MCBS has not yet been validated for blood cancer medicines, the European Haematology Association (EHA) has estimated a preliminary ESMO-MCBS score for some of these medicines. Where available, these EHA-estimated scores have been included in Table 5.7 (Kiesewetter et al 2020).

Table 5.7: Medicines funded in Australia and not in Aotearoa – haematology indications

Medicine	Indication per PBS	EHA MCBS estimate**	Pharmac status at time of analysis
Acalabrutinib	Chronic lymphocytic leukaemia/small lymphocytic leukaemia (relapsed/refractory, unsuitable for treatment with purine analogues)	N/A	Application received August 2021 Seeking clinical advice – this means Pharmac is seeking advice from external experts before this application is assessed and ranked against other options for investment https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P00000BLLor/p001721
Bendamustine	Follicular lymphoma (CD20 +ve, refractory to rituximab, re-induction) Used with obinutuzumab	N/A	No application received
Blinatumomab	Acute lymphoblastic leukaemia (B-precursor cell, relapsed/refractory, induction, consolidation and/or treatment of minimal residual disease)	5	No application received

Medicine	Indication per PBS	EHA MCBS estimate**	Pharmac status at time of analysis
Brentuximab vedotin	Anaplastic large cell lymphoma (CD30 +ve, relapsed/refractory, must be with curative intent)	2	Two related applications received January 2016 Both ranked as options for investment – this means that these options would be funded if the budget allowed. https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P00000BEvHl/p001678 https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P00000BHli7
Brentuximab vedotin	Hodgkin lymphoma (CD30 +ve, relapsed/refractory, post or unsuitable for autologous stem cell transplant)	N/A	Four related applications received January 2016 Three ranked as options for investment – this means that these options would be funded if the budget allowed. https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P000008pu9I https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P00000BHli7 https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P000008puiq One ranked as option for decline – this means this option would **not** be funded, even if budget allowed, unless new information came to light https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P000008puET/p000806
Brentuximab vedotin	T-cell lymphoma (cutaneous, CD30 +ve, relapsed/refractory)	N/A	No application received
Brentuximab vedotin	T-cell lymphoma (non-cutaneous, CD30 +ve, first-line, must be with curative intent) Used with chemotherapy	N/A	No application received

Medicine	Indication per PBS	EHA MCBS estimate**	Pharmac status at time of analysis
Carfilzomib	Multiple myeloma (relapsed/refractory, post or ineligible for stem cell transplant) Used with dexamethasone	4	Three related applications received August 2018 One ranked as an option for investment – this means that this would be funded if the budget allowed. Two seeking clinical advice – this means Pharmac is seeking advice from external experts before this application is assessed and ranked against other options for investment Note: At the time of publication, one of the pending applications had been ranked as an option for investment and the other is under assessment. This means that Pharmac has received clinical advice related to this application and is now assessing the application prior to ranking it against other options for investment. https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P000008pug4 https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P00000BIsC8 https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P00000BIsCD
Daratumumab	Multiple myeloma (relapsed/refractory, only one prior therapy) Used in combination with bortezomib and dexamethasone	3	Application received April 2021 Seeking clinical advice – this means Pharmac is seeking advice from external experts before this application is assessed and ranked against other options for investment Note: At the time of publication this application status had been updated to options compared. This option had been ranked as an option for investment– this means that this would be funded if the budget allowed. https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P00000BD0yw/p001671

Medicine	Indication per PBS	EHA MCBS estimate**	Pharmac status at time of analysis
Ibrutinib	Chronic lymphocytic leukaemia/small lymphocytic leukaemia (relapsed/refractory, unsuitable for treatment with purine analogues)	3	Three related applications received August 2015 Two ranked as options for investment – this means that these options would be funded if the budget allowed. One ranked as an option for decline – this means this option would **not** be funded, even if budget allowed, unless new information came to light https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P00000AaVR6/p001598 https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P00000AaVRQ/p001599 https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P00000AaVR6/p001598
Ibrutinib	Mantle cell lymphoma (relapsed/refractory)	3	Application received August 2015 Ranked as an option for investment – this means that this would be funded if the budget allowed. Note: At the time of publication this application status had been updated to seeking clinical advice. This means Pharmac is seeking further expert advice before it assesses and (re)ranks this application.
Idelalisib	Follicular B-cell non-Hodgkin lymphoma (relapsed/refractory)	3	No application received
Idelalisib	Chronic lymphocytic leukaemia/small lymphocytic leukaemia (CD20 +ve, relapsed/ refractory, inappropriate for chemo-immunotherapy)	N/A	No application received

Medicine	Indication per PBS	EHA MCBS estimate**	Pharmac status at time of analysis
Inotuzumab ozogamicin	Acute lymphoblastic leukaemia (B-precursor cell, relapsed/refractory, induction and consolidation	4	Two related applications received June 2021 Both seeking clinical advice. This means Pharmac is seeking further expert advice before it assesses and ranks these applications. https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P00000BK0rY/p001711 https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P00000BQ7JF/p001762
Lenalidomide	Multiple myeloma (in combination with bortezomib and dexamethasone, first-line)	4	Two related applications received May 2016 and May 2017. Both seeking clinical advice – this means Pharmac is seeking advice from external experts before these applications are assessed and ranked against other options for investment. Note: At the time of publication, this application status had been updated to under assessment – this means that Pharmac has received clinical advice regarding this funding application, and it is working to compare this against other options for funding. https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P000008pua9/p001248 https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P000008ptqe/p000072
Lenalidomide	Multiple myeloma (in combination with dexamethasone, transplant ineligible, first-line)	4	Application received May 2016. Seeking clinical advice – this means Pharmac is seeking advice from external experts before this application is assessed and ranked against other options for investment. Note: At the time of publication, this application status had been updated to under assessment – this means that Pharmac has received clinical advice regarding this funding application, and it is working to compare this against other options for funding. https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P00000BIsBt/p001695

Medicine	Indication per PBS	EHA MCBS estimate**	Pharmac status at time of analysis
Lenalidomide	Myelodysplastic syndrome (deletion 5q, low or intermediate-1 IPSS risk, red blood cell transfusion dependent, first-line)	2	No application received
Midostaurin	Acute myeloid leukaemia (ITD or TKD-FLT3 mutation +ve, induction, consolidation and/or maintenance)	A	Application received August 2019 Ranked as an option for investment – this means that this would be funded if the budget allowed. https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P000008ptwH/p000276
Obinutuzumab	Follicular lymphoma (CD20 +ve) Used with bendamustine	N/A	Application received February 2018 Seeking clinical advice. This means Pharmac is seeking expert advice before it assesses and ranks this application. https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P000008puZn/p001236
Obinutuzumab	Chronic lymphocytic leukaemia/small lymphocytic leukaemia (first-line, unsuitable for therapy with purine analogues) Used with venetoclax	N/A	Application received February 2020 Under assessment – this means that Pharmac has received clinical advice regarding this funding application, and it is working to compare this against other options for funding https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P000009sDbV/p001524
Pembrolizumab	Primary mediastinal B-cell lymphoma (relapsed/refractory, post or unsuitable for autologous stem cell transplant)	N/A	No application received

Medicine	Indication per PBS	EHA MCBS estimate**	Pharmac status at time of analysis
Pembrolizumab	Hodgkin lymphoma (relapsed/refractory, post or unsuitable for autologous stem cell transplant)	4	Three related applications received November 2017 Seeking clinical advice. This means Pharmac is seeking expert advice before it assesses and ranks this application. Note: At the time of publications these three applications had been updated to options compared. All three applications were ranked as options for investment – this means that these options would be funded if the budget allowed. https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P00000BLKJl/p001718 https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P00000BLKJv/p001719 https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P000008pu3x/p000527
Pomalidomide	Multiple myeloma (post or unsuitable for primary stem cell transplant and relapsed/refractory to other systemic treatments) Used with dexamethasone	N/A	Two related applications received November 2015 Both seeking clinical advice. This means Pharmac is seeking further expert advice before it assesses and ranks these applications. Note: At the time of publication these applications had been updated to under assessment. this means that Pharmac has received clinical advice regarding these funding applications, and it is working to compare these against other options for funding. https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P00000BIsCh/p001701 https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P00000BIsCc/p001700
Ponatinib	Acute lymphocytic leukaemia (second-line after prior systemic treatments)	2	No application received
Ponatinib	Chronic myeloid leukaemia (T3151 mutation positive, relapsed/refractory)	N/A	No application received

Medicine	Indication per PBS	EHA MCBS estimate**	Pharmac status at time of analysis
Pralatrexate	Peripheral T-cell lymphoma (relapsed/refractory)	N/A	No application received
Venetoclax	Chronic lymphocytic leukaemia/small lymphocytic leukaemia (first-line, unsuitable for therapy with purine analogues) Used with obinutuzumab	N/A	Application received February 2020 Under assessment – this means that Pharmac has received clinical advice regarding this funding application, and is working to compare it against other options for funding. https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P000009sDbV/p001524
Vorinostat	Cutaneous T-cell lymphoma (relapsed/ refractory, ineligible for stem cell transplant)	N/A	No application received

* Funded without restriction in Australia. Indications from TGA-approved product information and eviQ.

** No clinical assessment of the relevance of the comparator was made.

N/A: not available.

Appendix 6: Results table from comparison with Ontario, Canada

This appendix provides results from comparing the list of medicine-indication pair gaps for solid tumours in Aotearoa likely to have substantial clinical benefit with the same in Ontario, Canada. Table 6.1 outlines the funding status in Ontario for each gap.

Table 6.1: Comparison with Ontario, Canada

Indication	Medicine/regimen	Ontario funding status
Breast cancer (early-stage, HER-2+ve, adjuvant to neo-adjuvant trastuzumab with chemotherapy and surgery)	Trastuzumab emtansine	Funded (universally)
Melanoma (stage III or IV, adjuvant to surgery)	Nivolumab OR	Funded (universally)
	Pembrolizumab	Funded (universally)
Melanoma (stage III, BRAF +ve, adjuvant to surgery)	Dabrafenib + trametinib	Funded (not universally)
Lung cancer (non-small cell lung cancer (NSCLC), stage IV, first-line)	Atezolizumab + bevacizumab OR	Not funded
	Nivolumab + ipilimumab OR	Not funded (pharmaceutical company provides compassionate supply)
	Pembrolizumab	Funded (universally)
Lung cancer (non-small cell lung cancer (NSCLC), stage III, consolidation after chemoradiotherapy)	Durvalumab	Funded (universally)
Lung cancer (non-small cell lung cancer (NSCLC), locally advanced or metastatic, second-line)	Atezolizumab	Funded (universally)
	Nivolumab	Funded (universally)
Lung cancer (non-small cell lung cancer (NSCLC), stage IIIb or IV, EGFR+ve, first-line)	Osimertinib	Funded (not universally)
Lung cancer (non-small cell lung cancer (NSCLC), stage IIIb or IV, EGFR+ve T790M mutation, second-line)	Osimertinib	Funded (not universally)
Bowel cancer (colorectal cancer (CRC), metastatic, RAS wild-type, first-line	Cetuximab OR	Not funded
	Panitumumab	Not funded

Indication	Medicine/regimen	Ontario funding status
Bowel cancer (colorectal cancer (CRC), metastatic, RAS wild-type, second-line)	Cetuximab	Funded (universally) – only after 2 prior lines of treatment (ie, 3rd line)
Liver cancer (hepatocellular carcinoma (HCC), advanced (unresectable), Barcelona Clinic Liver Cancer stage B or C, first-line)	Atezolizumab + bevacizumab	Not funded
Kidney cancer (renal cell carcinoma (RCC), clear cell variant, stage IV, intermediate/poor risk, first-line)	Nivolumab + ipilimumab	Funded (universally)
Kidney cancer (renal cell carcinoma (RCC) clear cell variant, stage IV, second-line)	Nivolumab	Funded (universally)
Kidney cancer (renal cell carcinoma (RCC), clear cell variant, stage IV, second-line)	Axitinib	Funded (not universally)
Ovarian cancer (Epithelial ovarian, fallopian tube or primary peritoneal cancer, BRCA +ve [germline and/or somatic], first-lineline maintenance)	Olaparib	Funded (not universally)
Ovarian cancer (epithelial ovarian, fallopian tube or primary peritoneal cancer, second-line)	Bevacizumab	Funded (universally)
Bladder cancer (urothelial cancer, locally advanced or metastatic, second-line)	Pembrolizumab	Funded (universally)
Head and neck cancer (head and neck squamous cell carcinoma (HNSCC), locally recurrent or metastatic, second-line)	Nivolumab	Funded (universally)
Melanoma (stage III or IV, BRAF +ve, unresectable)	Dabrafenib and trametinib	Funded (not universally)
	Encorafenib + binimetinib	Not funded
	Vemurafenib +cobimetinib	Funded (not universally)
Melanoma (stage III or IV, unresectable, first-line induction)	Nivolumab + ipilimumab	Funded (universally)

Funded (not universally) = Medicines funded only for those eligible for the Ontario Drug Benefit (ODB) programme.

ODB eligible: Ontarians aged 65 years and older, residents of long-term care homes and homes for special care, recipients of professional home services and social assistance and recipients of Ontario's Trillium Drug Program (TDP) (ie, Ontario residents who have high drug costs in relation to their household income).

Funded (universally) = Medicines funded via Ontario's New Drug Funding Program for Cancer Care.

New Drug Funding Program for Cancer Care: Drug benefits for newer, intravenous drugs, typically administered in hospitals and cancer care facilities. The Ontario Ministry of Health provides about 75 percent of the overall funding for intravenous cancer drugs in Ontario, and hospitals fund the remaining 25 percent through their operating budgets.

Not funded = No public funding available.

For more information, see the Ontario Public Drug Programs webpage on the Ontario Ministry of Health, Ministry of Long-Term Care website at: www.health.gov.on.ca/en/pro/programs/drugs/funded_drug/funded_drug.aspx.

Appendix 7: Detailed descriptions of each identified gap associated with substantial clinical benefit

For each identified gap associated with substantial clinical benefit, this appendix provides a detailed description, organised by type of cancer. The table for each medicine-indication gap includes:

- the medicine class
- intent of treatment (whether curative or non-curative)
- where the gap is in the pipeline of Pharmac's assessment
- the associated ESMO-MCBS score for the gap
- how filling the gap would change current clinical practices
- the estimated size of the eligible population (if readily available)
- how the medicine would be given
- additional considerations for patients, whānau and the health system.

For each type of cancer where there were identified gaps, a broad population-level snapshot of the epidemiology of that cancer (its overall incidence, survival, mortality and known inequities across these aspects) is also provided.

Lung cancer

Table 7.1: Immunotherapy/immunochemotherapy for lung cancer – first-line therapy

Indication description	Non-small cell lung cancer, locally advanced or metastatic, as first-line therapy Note: PBS funding criteria do not mention PD-L1 status^
Medicine options to fill the gap	Atezolizumab with bevacizumab (used with chemotherapy) OR Nivolumab with ipilimumab (used with chemotherapy) OR Pembrolizumab (used with or without chemotherapy)
Description of medicine class'	Atezolizumab, nivolumab and pembrolizumab: immune checkpoint inhibitors (monoclonal antibodies targeting PD-1/PD-L1 proteins) Ipilimumab: immune checkpoint inhibitor (monoclonal antibody targeting CTLA-4 protein) Bevacizumab: targeted treatment (monoclonal antibody targeting VEGF protein)
Intent of treatment	Non-curative

Pharmac status at time of analysis	**Atezolizumab with bevacizumab** (used with chemotherapy) Application received November 2018 Ranked as an option for decline – this means this option would not be funded, even if budget allowed, unless new information came to light. Note: At the time of publication, Pharmac had updated the status of this application to seeking clinical advice. This means Pharmac is seeking further expert advice before it assesses and (re)ranks this application. https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P000008puFH/p000836
	Nivolumab with ipilimumab (used with chemotherapy) Pharmac has not received a funding application.
	Pembrolizumab (used without chemotherapy in patients with 'PD-L1 high' cancer) Application received February 2017 Ranked as an option for investment – this means that this option would be funded if the budget allowed. Note: At the time of publication, Pharmac had updated the status of this application to seeking clinical advice. This means Pharmac is seeking further expert advice before it assesses and (re)ranks this application. https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P000008pu56/p000583
	Pembrolizumab (used with chemotherapy in 'regardless of PD-L1' patient population) Application received August 2018. Ranked as an option for investment – this means that this option would be funded if the budget allowed. Note: At the time of publication, Pharmac had updated the status of this application to seeking clinical advice. This means Pharmac is seeking further expert advice before it assesses and (re)ranks this application. https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P000008puL2/p000911

ESMO-MCBS clinical benefit score and summary of data informing the score	Atezolizumab with bevacizumab (used with chemotherapy	3	Compared with bevacizumab (used with chemotherapy): Gain in median overall survival of 4.5 months Gain in median progression-free survival of 1.5 months Similar toxicities were noted – these did not contribute to the score. Quality-of-life results did not contribute to the score. Note: These were the results in a comparison against bevacizumab, which is not funded in Aotearoa. The relevant comparator for Aotearoa would be chemotherapy alone. Bevacizumab has been shown to improve overall survival by up to around two months when added to chemotherapy alone (Soria et al 2013). Therefore, this regimen was categorised as likely to score at least 4 in the Aotearoa setting. www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-155-1
	Nivolumab with ipilimumab (used with chemotherapy)	4	Compared with standard chemotherapy: Gain in median overall survival of 4.7 months Progression-free survival results did not contribute to the score. Quality-of-life and toxicity results did not contribute to the score. www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-257-1
	Pembrolizumab (used without chemotherapy in patients with 'PD-L1 high' cancer)	5	Compared with standard chemotherapy: Gain in median overall survival of 15.8 months Gain in median progression-free survival of 4.3 months Improved toxicity profile contributed to the score. Quality-of-life results did not contribute to the score. www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-68-1

Current clinical practice in Aotearoa and how this would change if the gap were filled	The current approach for these patients is treatment with chemotherapy (as definitive treatment with surgical resection or chemoradiation is not an option). If atezolizumab and bevacizumab, or nivolumab and ipilimumab were funded for use in this setting, they would be added on to chemotherapy. If pembrolizumab were funded in this setting, it would be added to chemotherapy or may be used on its own (ie, monotherapy) instead of chemotherapy, for people with 'PD-L1 high' cancer. Patients would only receive treatment with immune checkpoint inhibitors for one line of therapy, and clinical advice indicated that giving it earlier rather than later is generally preferred. This means that if this gap were filled, the gap for immune checkpoint inhibitors in the second line would become redundant (for people who received first-line immune checkpoint inhibitor treatment).
Pharmac estimate of eligible population size	Approximately 900 people per year, representing an 'all comers scenario' without PD-L1 testing
How these medicines would be given	These medicines are all given by infusion. For atezolizumab and bevacizumab, patients would receive four cycles of platinum-based chemotherapy with additional infusions each cycle of both atezolizumab and bevacizumab. After these four cycles, atezolizumab and bevacizumab would be given as intravenous infusions once every three weeks until disease progression or unacceptable toxicity. If bevacizumab is discontinued due to toxicity, atezolizumab may be continued as monotherapy. For nivolumab with ipilimumab, patients would have at least two to four cycles of platinum-based chemotherapy, with nivolumab and ipilimumab infusions in addition. Nivolumab and ipilimumab would then be given every three weeks until disease progression or unacceptable toxicity, for up to two years. For pembrolizumab used without chemotherapy, pembrolizumab would be given either once every three or six weeks until disease progression (or unacceptable toxicity), for up to two years. For pembrolizumab used with chemotherapy, patients would receive four cycles of platinum-based chemotherapy with an additional infusion each cycle of pembrolizumab. After four cycles, pembrolizumab would continue to be given once either every three or every six weeks until disease progression (or unacceptable toxicity), for up to two years.

Patient and whānau considerations	In general, this would be an additional treatment used together with (or in some cases instead of) standard chemotherapy treatment, with the potential clinical benefit described above. Unlike chemotherapy alone, where the treatments stop after a fixed amount of time, treatment would continue until there is progression of the disease, usually up to a maximum of two years. This would mean that, compared with current treatment, there would generally be more treatment appointments to attend and more follow-up visits. The treatments are generally administered in the outpatient infusion centre, so patients would need to travel, but there would be no prescription charge. There may be other medicines needed to manage side effects and these medicines may have a prescription charge. There are some particular side effects associated with immune checkpoint inhibitors that are quite different to the side effects of chemotherapy. These can develop long after treatment has stopped and may require specialised management.
Health system resource considerations	Additional treatment and follow-up appointments required. Additional chair time for administration of treatment. Increased demand for laboratory and pathology services to determine treatment eligibility and monitor for treatment toxicities. If these treatments were funded with the requirement to determine PD-1/PD-L1 status, this would have a particularly significant impact on pathology and laboratory services as these tests are not routinely available in Aotearoa. These tests may also require additional surgical intervention. Even if this is not required through funding criteria, there may still be a clinical need for testing to determine which patients could be treated with immunotherapy rather than immunochemotherapy. Increased demand for radiology services to assess for disease progression (subject to any funding criteria). Increased demand for supportive care and toxicity management (including health care professionals' time and pharmaceuticals).

^ In clinical trials of immunotherapies such as pembrolizumab, the regimens used and clinical efficacy differ based on PD-L1 status of the lung cancer. Pharmac has active funding applications both with and without regard to PD-L1 status. In Australia, immunotherapies are funded without requirements regarding PD-L1 status, and pembrolizumab may be used with or without concomitant chemotherapy. Therefore both 'PD-L1 high' and 'regardless of PD-L1 status' have been considered together as one group for the purpose of this analysis. For this gap to be filled in its entirety, the Pharmac funding criteria in Aotearoa would need to mirror those in Australia.

Table 7.2: Atezolizumab or nivolumab for lung cancer – second-line therapy

Indication description	Non-small cell lung cancer, locally advanced or metastatic, as second-line therapy		
Medicine option(s) to fill the gap	Atezolizumab OR Nivolumab		
Description of medicine class	Immune checkpoint inhibitor (monoclonal antibody targeting PD-1/PD-L1 protein)		
Intent of treatment	Non-curative		
Pharmac status at time of analysis	**Atezolizumab** Application received May 2017 Ranked as an option for investment – this means that this option would be funded if the budget allowed. Note: At the time of publication, Pharmac had updated the status to seeking clinical advice. This means Pharmac is seeking further expert advice before it assesses and (re)ranks this application. https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P000008ptuw/p000243		
	Nivolumab Application received February 2016 Ranked as an option for investment – this means that this option would be funded if the budget allowed. Note: At the time of publication, Pharmac had updated the status to seeking clinical advice. This means Pharmac is seeking further expert advice before it assesses and (re)ranks this application. https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P000008puDw/p000793		
ESMO-MCBS clinical benefit score and summary of data informing the score	Atezolizumab	5	Compared with standard chemotherapy: Gain in median overall survival of 4.2 months Progression-free survival results did not contribute to the score. Improved toxicity profile contributed to the score. Quality-of-life results did not contribute to the score. www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-126-1

ESMO-MCBS clinical benefit score and summary of data informing the score (continued)	Nivolumab	5	Compared with standard chemotherapy in non-squamous non-small cell lung cancer: Gain in median overall survival of 2.8 months, with durable response (two-year survival gain >10%) Progression-free survival results did not contribute to the score. Reduced frequency of severe adverse events contributed to the score Improved quality of life noted but did not contribute to the score. www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-56-1
		5	Compared with standard chemotherapy in squamous non-small cell lung cancer: Gain in median overall survival of 3.2 months, with durable response (two-year survival gain 15%) Gain in progression-free survival of 0.7 months Reduced frequency of severe adverse events contributed to the score. Quality-of-life results did not contribute to the score. www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-55-1
Current clinical practice in Aotearoa and how this would change if the gap were filled	The current approach for this group is either chemotherapy or best supportive care. If either atezolizumab or nivolumab were funded, it would become an additional line of therapy before chemotherapy. Patients would only receive treatment with immune checkpoint inhibitors for one line of therapy, and clinical advice indicated that giving it earlier rather than later is generally preferred. This means that if the first-line gap were filled, this gap for immune checkpoint inhibitors in the second line would become redundant (for people who received immune checkpoint inhibitor treatment in their first line of treatment).		
Pharmac estimate of eligible population size	Approximately 800 people per year		
How these medicines would be given	These medicines are given by infusion. Atezolizumab would be given once every three or four weeks until disease progression (or unacceptable toxicity). Nivolumab would be given once every two or four weeks until disease progression (or unacceptable toxicity).		

Patient and whānau considerations	In general, this would be an additional line of treatment over and above what would currently be given, with the potential clinical benefit described above. Unlike traditional chemotherapy (which would sometimes be given for these patients), where the treatment often stops after a fixed amount of time, treatment would continue until there is progression of the disease (or unacceptable toxicity). This would mean that, compared with current approaches, there may be more treatment appointments to attend and more follow-up visits. The treatments are generally administered in the outpatient infusion centre, so patients would need to travel, but there would be no prescription charge. There may be other medicines needed to manage side effects that may have a prescription charge. There are some particular side effects associated with immune checkpoint inhibitors that are quite different to the side effects of chemotherapy. These can develop long after treatment has stopped and may require specialised management.
Health system resource considerations	Additional treatment and follow-up appointments may be required. Additional chair time for administration of treatment may be required. Increased demand for laboratory and pathology services to determine treatment eligibility and monitor for treatment toxicities. Increased demand for radiology services to assess for disease progression (subject to any funding criteria). Increased demand for supportive care and toxicity management (including health care professionals' time and pharmaceuticals).

Table 7.3: Durvalumab for lung cancer – consolidation therapy

Indication description	Non-small cell lung cancer, stage III, consolidation after chemoradiotherapy
Medicine option to fill the gap	Durvalumab
Description of medicine class	Immune checkpoint inhibitor (monoclonal antibody targeting PD-1/PD-L1 protein)
Intent of treatment	Non-curative
Pharmac status at time of analysis	Application received February 2020 Ranked as an option for investment – this means that this option would be funded if the budget allowed. Note: At the time of publication, Pharmac had announced approval of this funding application. This means that this gap will be filled from 1 August 2022. https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P000009kZDh/p001500
ESMO-MCBS clinical benefit score and summary of data informing the score	4 Compared with placebo: Gain in median overall survival of 18.4 months, with durable response (four-year survival gain >13.3%) Gain in median progression-free survival of 11.6 months Differences in toxicity were not noted. No benefit in quality of life was observed. www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-170-1
Current clinical practice in Aotearoa and how this would change if the gap were filled	Current approach for these patients after they receive initial chemoradiotherapy is to 'watch and wait', ie, patients do not receive any consolidation treatment and are followed closely to detect tumour recurrence. If durvalumab were funded, this would become an active treatment option for consolidating the response to chemoradiotherapy.
Pharmac estimate of eligible population size	80 people in the first year, increasing up to 100 people each year after a few years (Pharmac 2021c)
How this medicine would be given	This medicine is given by infusion. Durvalumab would be given every two or four weeks until disease progression (or unacceptable toxicity), for a maximum of one year (Medsafe 2021).

Patient and whānau considerations	This would be an additional treatment compared with the current approach (which is to 'watch and wait'), with the potential clinical benefit described above. This would mean that, compared with the current approach, there would be more treatment appointments to attend and more follow-up visits. Durvalumab would be administered in the outpatient infusion centre, so patients would need to travel, but there would be no prescription charge. There may be other medicines needed to manage side effects that may have a prescription charge. There would be more side effects expected when compared to the current approach of no active treatment. There are some particular side effects associated with immune checkpoint inhibitors that are quite different to the side effects of chemotherapy. These can develop long after treatment has stopped and may require specialised management.
Health system resource considerations	Additional treatment appointments required. Additional follow-up appointments may be required. Additional chair time for administration of treatment required. Increased demand for laboratory and pathology services to determine treatment eligibility and monitor for treatment toxicities. Increased demand for radiology services to assess for disease progression (subject to any funding criteria). Increased demand for supportive care and toxicity management (including health care professionals' time and pharmaceuticals).

Table 7.4: Osimertinib for lung cancer – first-line therapy

Indication description	Non-small cell lung cancer, stage IIIb or IV, EGFR +ve, first-line therapy
Medicine option to fill the gap	Osimertinib
Description of medicine class	Tyrosine kinase inhibitor (small molecule targeting the EGFR protein)
Intent of treatment	Non-curative
Pharmac status at time of analysis	Application received December 2019 Under assessment – this means that Pharmac has received clinical advice regarding this funding application, and it is working to compare this against other options for funding. https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P000009sG55/p001526
ESMO-MCBS clinical benefit score and summary of data informing the score	4 Compared with erlotinib or gefitinib: Gain in median overall survival of 6.8 months Gain in median progression-free survival of 8.7 months Improved toxicity profile contributed to the score. No benefit in quality of life was observed. www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-123-1
Current clinical practice in Aotearoa and how this would change if the gap were filled	Current approach for these patients is a first-generation EGFR tyrosine kinase inhibitor – either gefitinib or erlotinib. If osimertinib were funded, it would replace these options. Patients would only receive treatment osimertinib for one line of therapy, and clinical advice indicated that giving it earlier rather than later is generally preferred. This means that if this gap were filled, the gap for osimertinib in the second line would become redundant (for people who received osimertinib in the first line setting).
Pharmac estimate of eligible population size	A final estimate of the eligible population size was not readily available at time of publication, however an estimate of uptake in the first year of funding is 200 people.
How this medicine would be given	This medicine is given orally. Osimertinib is a tablet that is generally taken once daily. Treatment is continued until disease progression (or unacceptable toxicity).
Patient and whānau considerations	This would replace the current treatment options, with the potential clinical benefit described above. Compared with the current treatment options, there would be minimal difference in terms of the practicalities of treatment. The tablets could be taken at home and would generally be dispensed by the local pharmacy – a prescription fee would be payable, as for the current treatment options. The increase in progression-free survival would mean that the tablets may need to be taken for a longer time, and there may be more follow-up appointments with the treatment team.

Health system resource considerations	Additional follow-up appointments may be required. Increased demand for laboratory and pathology services to monitor for treatment toxicities. EGFR testing for treatment eligibility would be required, but this would not be substantially different than that for the current funded treatment options. Increased demand for radiology services to assess for disease progression (subject to any funding criteria).

Table 7.5: Osimertinib for lung cancer – second-line therapy

Indication description	Non-small cell lung cancer, stage IIIb or IV, EGFR +ve, second-line therapy
Medicine option to fill the gap	Osimertinib
Description of medicine class	Tyrosine kinase inhibitor (small molecule targeting the EGFR protein)
Intent of treatment	Non-curative
Pharmac status at time of analysis	Application received November 2017 Under assessment – this means that Pharmac has received clinical advice regarding this funding application, and it is working to compare this against other options for funding. https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P000008ptxm/p000329
ESMO-MCBS clinical benefit score and summary of data informing the score	4 Compared with standard chemotherapy No gain in overall survival noted Gain in median progression-free survival of 5.7 months Improved toxicity profile contributed to the score. Improved patient-reported quality of life was noted. www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-123-1
Current clinical practice in Aotearoa and how this would change if the gap were filled	These patients would have previously received a first-generation EGFR tyrosine kinase inhibitor – either gefitinib or erlotinib – and developed a specific resistance mutation – T790M. The current approach for these patients is to treat with either chemotherapy or best supportive care. If osimertinib were funded for these patients, it would displace the current treatment options. That is, chemotherapy may still be used, but it would become the third line of treatment. Patients would only receive treatment osimertinib for one line of therapy, and clinical advice indicated that giving it earlier rather than later is generally preferred. This means that if the first-line gap were filled, this gap in the second line would become redundant (for people who received osimertinib in the first-line setting).
Pharmac estimate of eligible population size	A final estimate of the eligible population size was not readily available at time of publication, however an estimate of uptake in the first year of funding is 62 people.
How this medicine would be given	This medicine is given orally. Osimertinib is a tablet that is generally taken once daily. Treatment is continued until disease progression (or unacceptable toxicity).

Patient and whānau considerations	This would displace the current treatment options, with the potential clinical benefit described above. This would be an additional line of treatment, including for some people who would otherwise receive best supportive care. Compared with chemotherapy, which generally needs to be given in outpatient infusion centres, the tablets could be taken at home – this would reduce the travel and time burdens. The tablets would generally be dispensed by the local pharmacy – a prescription fee would be payable, unlike for chemotherapy. The medicines needed to manage side effects would be different. The increase in progression-free survival would mean that the tablets may need to be taken for a longer time, and there may be more follow-up appointments with the treatment team. The same chemotherapy may still be used eventually, but this would be after the disease has progressed with osimertinib. In order to determine eligibility for this medicine, a particular laboratory test would need to be done using a sample of the tumour – this might mean an extra surgical procedure.
Health system resource considerations	Fewer treatment appointments required (although these may occur later). More follow-up appointments may be required. Reduced chair time for administration of treatment (although this chair time may be needed later). Increased demand for laboratory and pathology services to determine treatment eligibility and monitor for treatment toxicities. In particular, molecular testing for the specific T790M mutation would be required. This molecular test is not currently routinely available in Aotearoa. Generally, this additional testing would require an additional tumour tissue sample, which would generally require some degree of surgical intervention. Increased demand for radiology services to assess for disease progression (subject to any funding criteria). Altered demand for supportive care and toxicity management (may increase or decrease – including health care professionals' time and pharmaceuticals).

Epidemiology of lung cancer

Incidence

Lung cancer is one of the most commonly diagnosed cancers in Aotearoa, with 2,381 people diagnosed with the disease in 2018, including 507 Māori (Te Aho o Te Kahu 2021a). Non-small cell lung cancer accounted for 70 percent of new primary diagnoses of lung cancer from 2015 to 2018 (67 percent for Māori, 76 percent for Pacific peoples, 88 percent for Asian, 70 percent for New Zealand European) (Te Aho o Te Kahu 2021b). Incidence of lung cancer as a whole is nearly four times higher for Māori compared with non-Māori (42 per 100,000 for Māori compared with 13 per 100,000 for non-Māori). Incidence in Pacific peoples is nearly two times higher compared with the non-Māori, non-Pacific, non-Asian population (23 per 100,000 compared with 12 per 100,000) (Te Aho o Te Kahu 2021a). Relevant to the osimertinib gaps above, a study in Aotearoa found that 22.5 percent of patients with non-small cell lung cancer who were tested for EGFR mutations between 2010 and 2017 were EGFR-mutation positive, with higher rates of EGFR mutation-positive disease in Pacific peoples, Asian populations and Māori (Aye et al 2021).

Stage at diagnosis

Based on New Zealand Cancer Registry data from 2007–2016, 13 percent of lung cancers diagnosed over this time were diagnosed at a 'regional' stage of disease, when the disease has spread around the region of origin (closest equivalent to stage III), and 45 percent were diagnosed as advanced. Of note, lung cancer staging data has a high proportion of cancers with 'missing' stage because of data quality issues. In general, cancers with unknown stage are likely to be more advanced (Gurney, Stanley, Jackson, et al 2020).

Survival

Overall, lung cancer has 19 percent survival at five years (Te Aho o Te Kahu 2021a). Aotearoa is sixth out of seven high-income countries for five-year survival (Arnold et al 2019). From 2007–2016 data, Māori patients with lung cancer were 30 percent more likely to die than non-Māori patients with lung cancer. Survival disparities between Māori and non-Māori were present across all stages of disease at diagnosis (Gurney, Stanley, McLeod, et al 2020). There is also poorer lung cancer survival with increasing deprivation (Te Aho o Te Kahu 2021a).

Mortality

Lung cancer is the leading cause of cancer death in Aotearoa: 1,781 deaths from lung cancer in 2017, including 368 Māori. Mortality rates for lung cancer are three times higher for Māori compared with non-Māori (32 per 100,000 compared with 10 per 100,000). Mortality from lung cancer in Pacific peoples is almost two times higher compared with the non-Māori, non-Pacific, non-Asian population (17 per 100,000 compared with 11 per 100,000) (Te Aho o Te Kahu 2021a).

Breast cancer

Table 7.6: Trastuzumab emtansine for early breast cancer

Indication description	Breast cancer, early stage, HER-2+ve, adjuvant to surgery plus neoadjuvant trastuzumab and chemotherapy, with residual disease	
Medicine option to fill the gap	Trastuzumab emtansine	
Description of medicine class	Targeted treatment (monoclonal antibody targeting the HER-2 protein, conjugated to a cytotoxic agent)	
Intent of treatment	Curative	
Pharmac status at time of analysis	Application received February 2020 Ranked as an option for investment – this means that this option would be funded if the budget allowed. https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P000009rn2n/p001522	
ESMO-MCBS clinical benefit score and summary of data informing the score	No score available at time of analysis – likely to score at least B	The following data comparing trastuzumab emtansine to trastuzumab (von Minckwitz et al 2018) contributed to the ESMO-MCBS score estimation: Invasive disease-free survival at three years 11% higher compared with trastuzumab (88.3% compared with 77.0%, HR 0.50 (95% CI, 0.39–0.64)). Toxicity disadvantage (did not impact on score estimation) 18.0% of patients discontinued trastuzumab emtansine due to toxicities, compared with 2.1% of patients receiving trastuzumab. Quality-of-life data were not reported in this publication. https://pubmed.ncbi.nlm.nih.gov/30516102/
Current clinical practice in Aotearoa and how this would change if the gap were filled	The current approach for these patients is to complete up to 12 months' treatment with trastuzumab (regardless of pathological response to neoadjuvant treatment), made up of neoadjuvant (pre-surgery) treatment as well as adjuvant (post-surgery) treatment. If this medicine were funded for the subset of patients that have residual disease detected after surgery, trastuzumab emtansine would replace trastuzumab for the adjuvant (post-surgery) part of the 12-month treatment period.	
Pharmac estimate of eligible population size	At least 110 people each year (CaTSoP 2020)	
How this medicine would be given	This medicine is given by infusion. Trastuzumab emtansine would be given every three weeks for about 10 months.	

Patient and whānau considerations	This would replace the current treatment, with the potential clinical benefit described above. Compared with the current treatment, there would be minimal difference in terms of the practicalities of treatment. The treatment would still require travel to an infusion centre every three weeks for about 10 months after surgery, with a similar number of follow-up appointments. This treatment is more likely to cause side effects than the current treatment.
Health system resource considerations	No substantial change to treatment, follow-up appointments or chair time for administration of treatment. Potentially increased demand for laboratory and pathology services to monitor for treatment toxicities. Increased demand for supportive care and toxicity management.

Epidemiology of breast cancer

Incidence

Breast cancer is the second most commonly diagnosed cancer in Aotearoa – with an average of 3,000 women, including 400 Māori (Te Aho o Te Kahu 2021a) and around 25 men diagnosed each year (Breast Cancer Foundation New Zealand 2022). The rate of breast cancer is higher for Māori (46 per 100,000, total population) compared with non-Māori (40 per 100,000). The rate of breast cancer is also higher among Pacific peoples (44 per 100,000) compared with the non-Māori, non-Pacific, non-Asian population (42 per 100,000) (Te Aho o Te Kahu 2021a). Around 15 percent of women with breast cancer will be HER-2+ve (Māori 18 percent; Pacific 24 percent; Asian 18 percent; non-Māori, non-Pacific, non-Asian 15 percent). However, it should be noted that HER-2 status is unknown for around 20 percent of breast cancer cases, so this proportion may be conservative (Breast Cancer Foundation New Zealand 2022).

Stage at diagnosis

Early-stage breast cancer includes ductal carcinoma in situ as well as breast cancers in stages I, II and IIIa. Around 80 percent of women with breast cancer are diagnosed with either stage I (43 percent Māori; 32 percent Pacific; 47 percent Asian; 60 percent non-Māori, non-Pacific, non-Asian) or stage II disease (Māori 38 percent; Pacific 38 percent; Asian 37 percent; non-Māori, non-Pacific, non-Asian 34 percent). Around 13 percent are diagnosed with stage III disease (Māori 14 percent; Pacific 19 percent; Asian 12 percent; non-Māori, non-Pacific, non-Asian 12 percent) and the remaining 5 percent with advanced disease (Breast Cancer Foundation New Zealand 2022).

Survival

Around 91 percent of those diagnosed with breast cancer (stage 1 or higher) will survive to five years (89 percent Māori, 87 percent Pacific). In terms of survival by stage of disease, data from the New Zealand Cancer Registry indicates that 99 percent of patients diagnosed with stage 1, 93 percent of those with stage II, 81 percent of those with stage III and 29 percent of those with stage IV will survive to five years (Breast Cancer Foundation New Zealand 2022).

From 2003–2020 data, Māori patients with breast cancer are 33 percent more likely and Pacific patients are 52 percent more likely to die than non-Māori, non-Pacific, non-Asian patients (Breast Cancer Foundation New Zealand 2022).

Mortality

On average over the last decade, there have been 638 female deaths each year from breast cancer, including 77 Māori (Gurney, Robson, et al 2020; Te Aho o Te Kahu 2021a). Mortality rates for breast cancer are higher among Māori (9 per 100,000) compared with non-Māori (6 per 100,000). The rate of breast cancer mortality is also higher for Pacific peoples (10 per 100,000) compared with the non-Māori, non-Pacific, non-Asian population (7 per 100,000) (Te Aho o Te Kahu 2021a).

Liver cancer

Table 7.7: Atezolizumab with bevacizumab for liver cancer

Indication description	Hepatocellular carcinoma (HCC), advanced stage, unresectable, first-line therapy
Medicine option to fill the gap	Atezolizumab with bevacizumab
Description of medicine class	Atezolizumab: immune checkpoint inhibitor (monoclonal antibody targeting PD-L1 protein) Bevacizumab: targeted treatment (monoclonal antibody targeting VEGF protein)
Intent of treatment	Non-curative
Pharmac status at time of analysis	Application received September 2020 Seeking clinical advice – this means that Pharmac is seeking expert advice before it assesses and ranks this application. Note: At the time of publication, Pharmac had ranked this application as an option for investment. This means that this option would be funded if the budget allowed. https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P00000AlzxU/p001618
ESMO-MCBS clinical benefit score and summary of data informing the score	5 Compared with sorafenib: Gain in median overall survival of 9.6 months Gain in median progression-free survival of 2.5 months Toxicities did not factor in the scoring. Improved quality of life associated with delayed deterioration contributed to the score. Note: These were the results in a comparison against sorafenib, which is not funded in Aotearoa for this indication. The relevant comparator for Aotearoa would be best supportive care. Clinical advice indicated that, against this comparator, the ESMO-MCBS score would likely be at least 4. www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-215-1
Current clinical practice in Aotearoa and how this would change if the gap were filled	The current approach for these patients is best supportive care – there is no active treatment option funded in Aotearoa. If this regimen were funded, this would become the first line of active treatment for these patients.
Pharmac estimate of eligible population size	Approximately 60–70 people each year (CaTSoP 2021).
How this medicine would be given	These medicines are both given by infusion. Both medicines would be given every three weeks until disease progression (or unacceptable toxicity).

Patient and whānau considerations	This would provide an active treatment option, where currently there is none, with the potential clinical benefit described above. This would mean that, compared with the current approach, there would be more treatment appointments to attend and more follow-up visits. Both medicines would be administered in the outpatient infusion centre, so patients would need to travel, but there would be no prescription charge. There may be other medicines needed to manage side effects that may have a prescription charge. This treatment is associated with an increased risk of potentially fatal gastro-oesophageal variceal bleeding. There are some particular side effects associated with immune checkpoint inhibitors that are quite different to the side effects of chemotherapy. These can develop long after treatment has stopped and may require specialised management.
Health system resource considerations	Additional treatment appointments required. Additional follow-up appointments required. Additional chair time for administration of treatment required. Increased demand for laboratory and pathology services to monitor for treatment toxicities. Increased demand for radiology services to assess for disease progression (subject to any funding criteria). Increased demand for supportive care and toxicity management (including health care professionals' time and pharmaceuticals).

Epidemiology of liver cancer

Incidence

Liver cancers, of which the vast majority are hepatocellular carcinomas, are the thirteenth most common cancer in Aotearoa (ninth most common for Māori) – with an average of 315 people diagnosed each year, including 66 Māori. Liver cancer is more common among males than females, with around two-thirds of all cases occurring among males (Gurney, Robson, et al 2020; Te Aho o Te Kahu 2021a). There are substantial disparities in the incidence of liver cancer between Māori and non-Māori, with the rate for Māori three times higher than that for non-Māori (7 per 100,000 for Māori, 2 per 100,000 for non-Māori) (Gurney, Robson, et al 2020). A similar pattern is seen for Pacific peoples, who have a rate of liver cancer of 8 per 100,000 compared with 2 per 100,000 for the non-Māori, non-Pacific, non-Asian population (Te Aho o Te Kahu 2021a).

Stage at diagnosis

Based on an audit of clinical notes between 2006 and 2008, more than one-third (34 percent Māori, 38 percent non-Māori) of liver cancers are diagnosed at an advanced stage (Chamberlain et al 2013).

Survival

Those diagnosed with liver cancer have approximately 20 percent survival at five years (20 percent Māori, 22 percent non-Māori (Te Aho o Te Kahu 2021a). From 2007–2016 data, Māori patients with liver cancer are 31 percent more likely to die than non-Māori patients with liver cancer (Gurney, Stanley, McLeod, et al 2020). Using staging data from the New Zealand Cancer Registry, survival disparities between Māori and non-Māori were found to be the strongest among those with either advanced or unstaged disease (Gurney, Stanley, McLeod, et al 2020).

Mortality

On average over the last decade, there have been 234 deaths each year from liver cancer, including 43 Māori (Gurney, Robson, et al 2020; Te Aho o Te Kahu 2021a). Mortality rates for liver cancer are nearly three times higher for Māori compared with non-Māori (5 per 100,000 Māori compared with 2 per 100,000 non-Māori). Mortality from liver cancer in Pacific peoples (6 per 100,000) is also higher compared with the non-Māori, non-Pacific, non-Asian population (2 per 100,000).

Bowel cancer

Table 7.8: Cetuximab or panitumumab for bowel cancer – first-line therapy

Indication description	Colorectal cancer (CRC), metastatic, RAS wild-type, first-line therapy		
Medicine option to fill the gap	Cetuximab (used in combination with chemotherapy) OR Panitumumab (used in combination with chemotherapy)		
Description of medicine class	Targeted therapy (monoclonal antibodies targeting the EGFR protein)		
Intent of treatment	Non-curative		
Pharmac status at time of analysis	**Cetuximab:** multiple applications received One application related to this gap is ranked as an option for investment – this means that this would be funded if the budget allowed. Two applications related to this gap are under consultation as options for decline – this means these would not be funded, even if budget allowed, unless new information came to light, and Pharmac is seeking feedback on declining this application. Note: At the time of publication, Pharmac status has been updated to 'decision made' for the two 'options for decline' applications. These two applications have now been declined. This means that Pharmac has decided these options will not be funded. This does not prevent Pharmac from reconsidering funding if new evidence or other relevant information becomes available. The other application remains an option for investment. https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P000008ptyE/p000352 https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P000008ptuD/p000218 https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P000008puV2/p001111		
	Panitumumab: no application received.		
ESMO-MCBS clinical benefit score and summary of data informing the score	Cetuximab (with chemotherapy)	4	Compared with standard chemotherapy: Gain in median overall survival of 8.2 months Gain in median progression-free survival of 3 months Toxicity and quality-of-life results did not contribute to this score. www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-17-1
	Panitumumab (with chemotherapy)	4	Compared with standard chemotherapy: Gain in median overall survival of 7.4 months Gain in median progression-free survival of 1.6 months Toxicity and quality-of-life results did not contribute to this score. www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-15-1

Current clinical practice in Aotearoa and how this would change if the gap were filled	In Aotearoa, the current treatment for these patients is chemotherapy. If either cetuximab or panitumumab were funded in the first-line setting, they would be used as an add-on to chemotherapy. Patients would only receive an EGFR inhibitor in one line of treatment, and clinical advice indicated that giving it earlier rather than later is generally preferred. This means that if this gap were filled, the gap for cetuximab in the second line would become redundant (for people who received cetuximab or panitumumab in the first-line setting).
Pharmac estimate of eligible population size	Approximately 70 people each year (CaTSoP 2019).
How this medicine would be given	These medicines are both given by infusion. They would generally be given once every two weeks, on the same day as chemotherapy.
Patient and whānau considerations	In general, this would be an additional treatment used together with standard chemotherapy treatment, with the potential clinical benefit described above. Treatment would continue until there is progression of the disease (or intolerable side effects). This would mean that, compared with current treatment, there would generally be a similar number of treatment appointments to attend, but these appointments would last longer. The treatments are generally administered in the outpatient infusion centre, so patients would need to travel a similar amount to the current treatment, but there would be no prescription charge. There may be other medicines needed to manage side effects that may have a prescription charge. In order to determine eligibility for this medicine, a particular laboratory test would need to be done using a sample of the tumour – this might mean an extra surgical procedure.
Health system resource considerations	Additional chair time for administration of treatment required. Increased demand for laboratory and pathology services to determine eligibility for treatment and monitor for treatment toxicities. Specifically, molecular testing would be required to determine RAS mutational status. This testing is not routinely available in Aotearoa. A tissue sample would be required which may require additional surgical intervention for sample acquisition. Increased demand for radiology services to assess for disease progression (subject to any funding criteria). Potential for increased demand for supportive care and toxicity management (including health care professionals' time and pharmaceuticals).

Table 7.9: Cetuximab for bowel cancer – second-line therapy

Indication description	Colorectal cancer (CRC), metastatic, RAS wild-type, second-line therapy
Medicine option to fill the gap	Cetuximab
Description of medicine class	Targeted therapy (monoclonal antibody targeting the EGFR protein)
Intent of treatment	Non-curative
Pharmac status at time of analysis	Application received May 2013 Under consultation as an option for decline – this means this option would not be funded, even if budget allowed, unless new information came to light, and Pharmac is seeking feedback on declining this application. Note: At the time of publication, Pharmac status has been updated to decision made for this application – it has been declined. This means that Pharmac has decided this option will not be funded. This does not prevent Pharmac from reconsidering funding if new evidence or other relevant information becomes available. https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P000008pttC/p000175
ESMO-MCBS clinical benefit score and summary of data informing the score	4 Compared with best supportive care: Gain in median overall survival of 4.7 months Gain in median progression-free survival of 1.8 months Toxicity and quality-of-life results did not contribute to this score. www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-18-1
Current clinical practice in Aotearoa and how this would change if the gap were filled	In Aotearoa, the current treatment for these patients is chemotherapy or best supportive care. Either cetuximab or panitumumab in this setting would be used either alone or as an add-on to chemotherapy. Patients would only receive an EGFR inhibitor in one line of treatment, and clinical advice indicated that giving it earlier rather than later is generally preferred. This means that if the first-line gap were filled with cetuximab or panitumumab, this gap in the second line would become redundant (for people who received cetuximab or panitumumab in the first-line setting).
Pharmac estimate of eligible population size	A Pharmac estimate of the eligible population size was not readily available at time of publication.
How this medicine would be given	This medicine is given by infusion. Cetuximab would generally be given once every two weeks. For those patients receiving chemotherapy, cetuximab would usually be given on the same day.

Patient and whānau considerations	In general, this would be an additional treatment used together with standard chemotherapy treatment, or an additional line of treatment for people who would not tolerate chemotherapy, with the potential clinical benefit described above. Treatment would continue until there is progression of the disease (or intolerable side effects). This would mean that, compared with current treatment, there would be a similar number of treatment appointments to attend for those patients receiving chemotherapy, but these appointments would last longer. For patients receiving cetuximab as monotherapy, this would mean additional fortnightly treatment visits that otherwise would not have happened. Cetuximab would be administered in the outpatient infusion centre, so patients would need to travel, but there would be no prescription charge. There may be other medicines needed to manage side effects that may have a prescription charge. In order to determine eligibility for this medicine, a particular laboratory test would need to be done using a sample of the tumour – this might mean an extra surgical procedure.
Health system resource considerations	Additional treatment appointments required (at least for monotherapy). Additional follow-up appointments required (at least for monotherapy). Additional chair time for administration of treatment required. Increased demand for laboratory and pathology services to determine eligibility for treatment and monitor for treatment toxicities. Specifically, molecular testing would be required to determine RAS mutational status. This testing is not routinely available in Aotearoa. A tissue sample would be required which may require additional surgical intervention for sample acquisition. Increased demand for radiology services to assess for disease progression (subject to any funding criteria). Potential for increased demand for supportive care and toxicity management (including health care professionals' time and pharmaceuticals).

Epidemiology of bowel cancer

Incidence

Colorectal cancers are the third most commonly diagnosed cancers in Aotearoa – with an average of 3,000 people diagnosed each year, including 184 Māori (Te Aho o Te Kahu 2021a). The rate of colorectal cancer is lower for Māori (19 per 100,000) compared with non-Māori (24 per 100,000). The rate of colorectal cancer is also lower among Pacific peoples (18 per 100,000) compared with the non-Māori, non-Pacific, non-Asian population (25 per 100,000).

Stage at diagnosis

A clinical audit of all cases of colorectal cancer diagnosed in Aotearoa in 2007–2008 identified that around three-quarters (75 percent) of patients with colon or rectal cancer are diagnosed with stage I, II or III disease, with most of the remaining 25 percent diagnosed with stage IV (metastatic) disease. Māori appear to be more likely to be diagnosed with metastatic disease (29 percent colon, 29 percent rectal) than non-Māori, non-Pacific peoples (22 percent colon, 18 percent rectal) (Jackson et al 2015).

Survival

Around half of those diagnosed with colorectal cancer will survive to five years (colon: 53 percent Māori, 61 percent non-Māori; rectal: 55 percent Māori, 67 percent non-Māori) (Gurney, Stanley, McLeod, et al 2020). Aotearoa is fifth out of seven high-income countries for five-year survival from colorectal cancer (Arnold et al 2019). More than 90 percent of those diagnosed with localised colorectal cancer will survive to five years (94 percent colon, 93 percent rectal), compared with 74 percent of those with regional disease (both colon and rectal) and around 10 percent of those with advanced disease (13 percent colon, 10 percent rectal) (Araghi et al 2021). Based on data from 2007–2016, Māori patients with colorectal cancer are more likely to die from their cancer than non-Māori patients with colorectal cancer (colon: 46 percent more likely; rectal: 72 percent more likely) (Gurney, Stanley, McLeod, et al 2020).

Mortality

On average over the last decade, there have been 1,230 deaths each year from colorectal cancer, including 70 Māori (Gurney, Robson, et al 2020; Te Aho o Te Kahu 2021a). Mortality rates for colorectal cancer are lower among Māori (7 per 100,000) compared with non-Māori (8 per 100,000). The colorectal cancer mortality rate is also lower for Pacific peoples (7 per 100,000) compared with the non-Māori, non-Pacific, non-Asian population (10 per 100,000) (Te Aho o Te Kahu 2021a).

Kidney cancer

Table 7.10: Nivolumab with ipilimumab for kidney cancer – first-line therapy

Indication description	Renal cell carcinoma (RCC), clear cell variant, stage IV, intermediate/poor risk, first-line therapy
Medicine option to fill the gap	Nivolumab with ipilimumab
Description of medicine class	Nivolumab: immune checkpoint inhibitor (monoclonal antibody targeting PD-1 protein) Ipilimumab: immune checkpoint inhibitor (monoclonal antibody targeting CTLA-4 protein)
Intent of treatment	Non-curative
Pharmac status at time of analysis	No application received.
ESMO-MCBS clinical benefit score and summary of data informing the score	4 Compared with sunitinib: Gain in median overall survival of 21.5 months Progression-free survival results did not contribute to the score. Toxicity and quality-of-life results did not contribute to the score. www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-117-1
Current clinical practice in Aotearoa and how this would change if the gap were filled	In Aotearoa, the current treatment for these patients is a tyrosine kinase inhibitor (either sunitinib or pazopanib). If nivolumab with ipilimumab were funded for this indication, it would replace sunitinib/pazopanib for some people. However, nivolumab with ipilimumab may not be suitable for all patients. Patients would only receive immune checkpoint inhibitor treatment in one line of therapy, and clinical advice indicated that giving it earlier rather than later is generally preferred. This means that if this gap were funded, the gap for nivolumab in the second line would become redundant (for those people who received nivolumab with ipilimumab in the first line).
Pharmac estimate of eligible population size	A Pharmac estimate of the eligible population size was not readily available at time of publication. An approximation was calculated by using the average number of people diagnosed with kidney cancer, applying the proportion likely to be clear-cell, and then applying the proportion diagnosed at an advanced stage (see 'epidemiology of kidney cancer' section below). Based on this, the size of the eligible population was likely to be under 95 people per year [540*80%*22%=95], as this calculation did not take into account the proportion at intermediate/poor risk.
How this medicine would be given	These medicines are given by infusion. For the first three months of treatment, ipilimumab and nivolumab would be given every three weeks on the same day. After that, no more ipilimumab would be given, but treatment with nivolumab would continue – given every two to four weeks – until disease progression (or unacceptable toxicity).

Patient and whānau considerations	This treatment would replace the current treatment options (either sunitinib or pazopanib), with the potential clinical benefit described above. The current treatment is a tablet that can be taken at home, whereas nivolumab and ipilimumab are given as an infusion. This would mean that, compared with the current approach, there would be more treatment appointments to attend. Both medicines would be administered in the outpatient infusion centre, so patients would need to travel, but there would be no prescription charge. There may be other medicines needed to manage side effects that may have a prescription charge. There are some particular side effects associated with immune checkpoint inhibitors that are quite different to the side effects of chemotherapy. These can develop long after treatment has stopped and may require specialised management. Treatment would continue until there is progression of the disease (or intolerable side effects).
Health system resource considerations	Additional treatment appointments required. Additional follow-up appointments required. Additional chair time for administration of treatment required. Increased demand for laboratory and pathology services to determine eligibility for treatment and monitor for treatment toxicities. Increased demand for radiology services to assess for disease progression (subject to any funding criteria). Potential for increased demand for supportive care and toxicity management (including health care professionals' time and pharmaceuticals).

Table 7.11: Nivolumab for kidney cancer – second-line therapy

Indication description	Renal cell carcinoma (RCC), clear cell variant, stage IV, second-line therapy
Medicine option to fill the gap	Nivolumab
Description of medicine class	Immune checkpoint inhibitor (monoclonal antibody targeting PD-1 protein)
Intent of treatment	Non-curative
Pharmac status at time of analysis	Application received May 2017 Ranked as an option for investment. This means that this option would be funded if the budget allowed. https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P000008puZW/p001229
ESMO-MCBS clinical benefit score and summary of data informing the score	5 Compared with everolimus: Gain in median overall survival of 5.4 months Progression-free survival did not contribute to the score. Quality-of-life improvement noted. Reduced frequency of severe adverse events contributed to the score. Note: This was the score in a comparison against everolimus, which is not funded in Aotearoa for this indication. The relevant comparator for Aotearoa is best supportive care. Clinical advice indicated that nivolumab is likely more effective compared with best supportive care than with an active comparator. However, there may be more toxicities. Considered likely to score at least 4 in a comparison against best supportive care. www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-103-1
Current clinical practice in Aotearoa and how this would change if the gap were filled	In Aotearoa, the current treatment for these patients is best supportive care. If nivolumab were funded for this indication, it would become an active treatment option for people who received a tyrosine kinase inhibitor in the first line. Patients would only receive immune checkpoint inhibitor treatment in one line of therapy, and clinical advice indicated that giving it earlier rather than later is generally preferred. This means that if the first-line gap were funded, this gap for nivolumab in the second line would become redundant (for those people who received nivolumab with ipilimumab in the first line).
Pharmac estimate of eligible population size	Estimated at 120 people in the first year of funding, and then 60 people per year in the following years.
How this medicine would be given	This medicine is given by infusion. Nivolumab would be given every two to four weeks until disease progression (or unacceptable toxicity).

Patient and whānau considerations	This treatment would become an active treatment option for these patients, with the potential clinical benefit described above. The current approach is best supportive care. This would mean that, compared with the current approach, there would be more treatment appointments to attend. Nivolumab would be administered in the outpatient infusion centre, so patients would need to travel, but there would be no prescription charge. There may be other medicines needed to manage side effects that may have a prescription charge. There are some particular side effects associated with immune checkpoint inhibitors that are quite different to the side effects of chemotherapy. These can develop long after treatment has stopped and may require specialised management. Treatment would continue until there is progression of the disease (or intolerable side effects).
Health system resource considerations	Additional treatment appointments required. Additional follow-up appointments required. Additional chair time for administration of treatment required. Increased demand for laboratory and pathology services to determine eligibility for treatment and monitor for treatment toxicities. Increased demand for radiology services to assess for disease progression (subject to any funding criteria). Potential for increased demand for supportive care and toxicity management (including health care professionals' time and pharmaceuticals).

Table 7.12: Axitinib for kidney cancer – second-line therapy

Indication description	Renal cell carcinoma (RCC), clear cell variant, stage IV, second-line therapy
Medicine option to fill the gap	Axitinib
Description of medicine class	Targeted treatment (tyrosine kinase inhibitor targeting multiple VEGF receptor proteins)
Intent of treatment	Non-curative
Pharmac status at time of analysis	Application received September 2013. Ranked as an option for investment. This means that this option would be funded if the budget allowed. https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P000008pu4I/p000543
ESMO-MCBS clinical benefit score and summary of data informing the score	4 Compared with sorafenib: Gain in median overall survival of 0.9 months Gain in median progression-free survival of two months No quality-of-life benefit. Reduced frequency of severe adverse events contributed to the score. Note: This was the score in a comparison against sorafenib, which is not funded in Aotearoa for this indication. The relevant comparator for Aotearoa is best supportive care. Clinical advice indicated that axitinib is likely more effective compared with best supportive care than with an active comparator. However, there may be more toxicities. Considered likely to score at least 4 in a comparison against best supportive care. www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-104-1
Current clinical practice in Aotearoa and how this would change if the gap were filled	In Aotearoa, the current treatment for these patients is best supportive care. If axitinib were funded for this indication, it would become an active treatment option for people who received a tyrosine kinase inhibitor in the first line.
Pharmac estimate of eligible population size	Estimated at 120 people in the first year of funding, and then 60 people per year in the following years.
How this medicine would be given	This medicine is given orally. Axitinib is a tablet that is generally taken twice daily – more than one tablet may need to be taken for each dose. Treatment is continued until disease progression (or unacceptable toxicity).

Patient and whānau considerations	This treatment would become an active treatment option for these patients, with the potential clinical benefit described above. The current approach is best supportive care. This would mean that, compared with the current approach, there would be tablets to take. These could be taken at home, but a prescription charge would be payable. There would be more follow-up appointments needed. There may be other medicines needed to manage side effects that may also have a prescription charge. Treatment would continue until there is progression of the disease (or intolerable side effects).
Health system resource considerations	Additional follow-up appointments required. Increased demand for laboratory and pathology services to determine eligibility for treatment and monitor for treatment toxicities. Increased demand for radiology services to assess for disease progression (subject to any funding criteria). Potential for increased demand for supportive care and toxicity management (including health care professionals' time and pharmaceuticals).

Epidemiology of kidney cancer

Incidence

Kidney cancers, of which the vast majority are renal cell cancers, are among the top-10 most commonly diagnosed cancers in Aotearoa – with an average of 540 people diagnosed each year, including 60 Māori (Te Aho o Te Kahu 2021a). Internationally, clear cell renal cell cancers make up about 80 percent of all renal cell cancers (National Cancer Institute 2020). The rate of kidney cancer is somewhat higher for Māori (7 per 100,000) compared with non-Māori (5 per 100,000 for non-Māori – Te Aho o Te Kahu 2021a). By contrast, the rate of kidney cancer among Pacific peoples is lower than that of the non-Māori, non-Pacific, non-Asian population (Meredith et al 2012).

Stage at diagnosis

Based on New Zealand Cancer Registry data, the majority of kidney cancers are diagnosed at either the local stage (43 percent of total cases, 34 percent Māori, 42 percent New Zealand European) or a 'regional' stage, when the disease has spread around the region of origin (16 percent total, 13 percent Māori, 17 percent New Zealand European). Around one-quarter of kidney cancers are diagnosed at an advanced stage (22 percent total, 25 percent Māori, 22 percent New Zealand European), while around 20 percent remain unstaged on the registry (19 percent total, 28 percent Māori, 19 percent New Zealand European) (Gurney, Stanley, Jackson, et al 2020).

Survival

Around two-thirds of those diagnosed with kidney cancer will survive to five years (62 percent Māori, 68 percent non-Māori (Gurney, Stanley, McLeod, et al., 2020). There is currently a lack of robust stage-specific survival data for kidney cancer in Aotearoa. From 2007–2016 data, Māori patients with kidney cancer are 63 percent more likely to die than non-Māori patients with kidney cancer (Gurney, Stanley, McLeod, et al 2020).

Mortality

On average over the last decade, there have been 190 deaths each year from kidney cancer, including 19 Māori (Gurney, Robson, et al 2020; Te Aho o Te Kahu 2021a). Mortality rates for kidney cancer are somewhat higher for Māori (2 per 100,000) compared with non-Māori (1 per 100,000) (Robson et al 2010). By contrast, kidney cancer mortality rates are lower for Pacific peoples (1 per 100,000) than for the non-Māori, non-Pacific, non-Asian population (2 per 100,000) (Te Aho o Te Kahu 2021a).

Bladder cancer

Table 7.13: Pembrolizumab for bladder cancer

Indication description	Urothelial cancer, locally advanced or metastatic, second-line therapy
Medicine option to fill the gap	Pembrolizumab
Description of medicine class	Immune checkpoint inhibitor (monoclonal antibody targeting PD-1 protein)
Intent of treatment	Non-curative
Pharmac status at time of analysis	Application received November 2017 Ranked as an option for investment. This means that this option would be funded if the budget allowed. https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P000008pu1w/p000485
ESMO-MCBS clinical benefit score and summary of data informing the score	4 Compared with chemotherapy: Gain in median overall survival of 2.9 months Progression-free survival did not contribute to the score. No quality-of-life improvement noted. Reduced frequency of severe adverse events contributed to the score. www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-278-1
Current clinical practice in Aotearoa and how this would change if the gap were filled	In Aotearoa, the current treatment for these patients is chemotherapy or best supportive care. If pembrolizumab were funded for this indication, it would become an additional line of active treatment. It would be used alone rather than being added to chemotherapy.
Pharmac estimate of eligible population size	Size of eligible population: approximately 50 people each year (CaTSoP 2019).
How this medicine would be given	This medicine is given by infusion. Pembrolizumab would be given every three to six weeks until disease progression (or unacceptable toxicity).
Patient and whānau considerations	This treatment would become an additional treatment option for these patients, with the potential clinical benefit described above. The current approach is either chemotherapy or best supportive care. This would mean that, compared with the current approach, there would generally be more treatment appointments to attend. Pembrolizumab would be administered in the outpatient infusion centre once every three or six weeks, so patients would need to travel, but there would be no prescription charge. There may be other medicines needed to manage side effects that may have a prescription charge. There are some particular side effects associated with immune checkpoint inhibitors that are quite different to the side effects of chemotherapy. These can develop long after treatment has stopped and may require specialised management. Treatment would continue until there is progression of the disease (or intolerable side effects).

Health system resource considerations	Additional treatment appointments may be required. Additional follow-up appointments required. Additional chair time for administration of treatment may be required. Increased demand for laboratory and pathology services to monitor for treatment toxicities. Increased demand for radiology services to assess for disease progression (subject to any funding criteria). Potential for increased demand for supportive care and toxicity management (including health care professionals' time and pharmaceuticals).

Epidemiology of bladder cancer

Incidence

Bladder cancers, of which the vast majority are urothelial cancers, are the fourteenth most commonly diagnosed cancers in Aotearoa – with an average of 380 people diagnosed each year, including 24 Māori (Te Aho o Te Kahu 2021a). The rate of bladder cancer is somewhat lower for Māori (3 per 100,000) compared with non-Māori (4 per 100,000) (Robson et al 2010). The rate of bladder cancer is also lower among Pacific peoples compared with the non-Māori, non-Pacific, non-Asian population (Meredith et al 2012).

Stage at diagnosis

There is currently a lack of national, robust staging information available for bladder cancer in Aotearoa, and the vast majority of bladder cancers remain unstaged on the New Zealand Cancer Registry (70 percent of total cases, 65 percent Māori, 66 percent New Zealand European). Approximately 12 percent are listed on the registry as having advanced disease (12 percent total, 11 percent Māori, 12 percent New Zealand European), with the remaining 18 percent listed as having either local (7 percent) or regional (11 percent) disease (Gurney, Stanley, Jackson, et al 2020).

Survival

Around half of those diagnosed with bladder cancer will survive to five years (43 percent Māori, 52 percent non-Māori) (Gurney, Stanley, McLeod, et al 2020). There is currently a lack of robust stage-specific survival data for bladder cancer in Aotearoa. From 2007–2016 data, Māori patients with bladder cancer are 37 percent more likely to die from that cancer than non-Māori patients with bladder cancer (Gurney, Stanley, McLeod, et al 2020).

Mortality

On average over the last decade, there have been 202 deaths each year from bladder cancer, including 11 Māori (Gurney, Robson, et al 2020; Te Aho o Te Kahu 2021a). Mortality rates for bladder cancer are similar between Māori and non-Māori (both 1 per 100,000) (Robson et al 2010). The bladder cancer mortality rate is also similar for Pacific peoples compared with the non-Māori, non-Pacific, non-Asian population (both 1 per 100,000) (Te Aho o Te Kahu 2021a).

Ovarian cancer

Table 7.14: Olaparib for ovarian cancer

Indication description	Epithelial ovarian, fallopian tube or primary peritoneal cancer, stage IIIb or IV, BRCA +ve (germline or somatic), first-line maintenance therapy
Medicine option to fill the gap	Olaparib
Description of medicine class	Targeted treatment (small molecule PARP inhibitor targeting BRCA mutated cells)
Intent of treatment	Non-curative
Pharmac status at time of analysis	Application received May 2020. Ranked as an option for investment. This means that this option would be funded if the budget allowed. Note: At the time of publication, Pharmac had announced approval for this funding application. This means that this gap will be filled (for germline BRCA+ve ovarian cancer) from 1 August 2022. A gap for somatic BRCA+ve ovarian cancer will remain. https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P00000AHK3i/p001558
ESMO-MCBS clinical benefit score and summary of data informing the score	4 Compared with placebo: Gain in overall survival not reported Gain in median progression-free survival of over 30 months with durable response (two-year progression-free survival gain >10%) No quality-of-life benefit. Toxicity results did not contribute to the score. www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-144-1
Current clinical practice in Aotearoa and how this would change if the gap were filled	In Aotearoa, the current treatment for these patients is 'watch and wait' following first-line chemotherapy. This means that patients do not receive any active maintenance treatment after their first line of chemotherapy, and are followed closely to detect tumour recurrence. If olaparib were funded for this indication, it would become an active maintenance treatment option for people who received platinum-based chemotherapy that reduced or cleared the cancer.
Pharmac estimate of eligible population size	Size of eligible population: approximately 20 people in the first year, increasing over time (Pharmac 2021c).
How this medicine would be given	This medicine is given orally. Olaparib is a tablet that is generally taken twice daily – the standard dosing is eight capsules taken for each dose. Treatment is continued for two years (or until disease progression or unacceptable toxicity). If the tumour is not in complete response at the end of two years, treatment may continue.

Patient and whānau considerations	This treatment would become an active maintenance treatment option for these patients, with the potential clinical benefit described above. Compared with the current approach ('watch and wait'), there would be tablets to take. These could be taken at home, but a prescription charge would be payable. There would be more follow-up appointments needed. There may be other medicines needed to manage side effects that may also have a prescription charge. Treatment would continue for two years unless there the disease progressed (or there were intolerable side effects). If there was still evidence of the tumour after two years, treatment could continue. This medicine may require a particular genetic test prior to funded access. Because this genetic test looks at a patient's inherited genetic profile, there may be implications of this testing to other members of the whānau that need to be considered.
Health system resource considerations	Additional follow-up appointments required. Increased demand for clinical genetics services to determine eligibility for treatment (via germline mutations), and to assess familial cancer risk. Increased demand for laboratory and pathology services to determine eligibility for treatment and monitor for treatment toxicities. In particular, there would be increased requirements for molecular testing for BRCA mutations – either germline or somatic. Currently, there are capacity constraints on germline BRCA testing, and somatic BRCA testing is not routinely available in Aotearoa. Increased demand for radiology services to assess for disease progression (subject to any funding criteria). Potential for increased demand for supportive care and toxicity management (including health care professionals' time and pharmaceuticals).

Table 7.15: Bevacizumab for ovarian cancer

Indication description	Epithelial ovarian, fallopian tube or primary peritoneal cancer, metastatic, recurrent, platinum-resistant
Medicine option to fill the gap	Bevacizumab (used with chemotherapy)
Description of medicine class	Targeted treatment (monoclonal antibody targeting VEGF protein)
Intent of treatment	Non-curative
Pharmac status at time of analysis	Application received November 2013 Under consultation as an option for decline – this means this option would not be funded, even if budget allowed, unless new information came to light, and Pharmac is seeking feedback on declining this application. Note: At the time of publication, Pharmac had updated the status to 'seeking clinical advice'. Consultation feedback indicated that there was updated information to be considered. Pharmac will now seek further advice. https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P000008pufP/p001366
ESMO-MCBS clinical benefit score and summary of data informing the score	4 Compared with chemotherapy: No gain in overall survival Gain in median progression-free survival of 3.3 months Quality-of-life improvement contributed to the score. Toxicity results did not contribute to the score. www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-37-1
Current clinical practice in Aotearoa and how this would change if the gap were filled	In Aotearoa, the current treatment for these patients is chemotherapy. If bevacizumab were funded for this indication, it would be added to chemotherapy.
Pharmac estimate of eligible population size	A Pharmac estimate of the eligible population size was not readily available at time of publication. The population size was not able to be estimated by other means. For reference purposes only, 280 people are diagnosed with ovarian cancer on average per year in Aotearoa, and about 60% (equating to 168 people) are diagnosed at an advanced stage (approximating metastatic here), see 'epidemiology of ovarian cancer' section below. It is unclear what proportion of these people would have recurrent, platinum-resistant disease.
How this medicine would be given	This medicine is given by infusion. Bevacizumab would be given once every two or three weeks (depending on the accompanying chemotherapy). Bevacizumab would usually be given on the same day as chemotherapy. Treatment would continue until disease progression (or unacceptable toxicity).

Patient and whānau considerations	This treatment would be added to the current treatment for these patients, with the potential clinical benefit described above. The current approach is chemotherapy, and bevacizumab would be added in. This would mean that, compared with the current approach, there would be a similar number of treatment appointments to attend. Bevacizumab would be administered in the outpatient infusion centre, on the same day as chemotherapy, so the appointment time would be longer. There may be other medicines needed to manage side effects that may have a prescription charge. Treatment would continue until there is progression of the disease (or intolerable side effects).
Health system resource considerations	Additional treatment and follow-up appointments may be required. Additional chair time for administration of treatment required. Increased demand for laboratory and pathology services to monitor for treatment toxicities. Increased demand for radiology services to assess for disease progression (subject to any funding criteria). Potential for increased demand for supportive care and toxicity management (including health care professionals' time and pharmaceuticals).

Epidemiology of ovarian cancer

Incidence

Ovarian cancer is the seventh most common cancer diagnosed among women in Aotearoa – with an average of 280 people diagnosed each year, including 32 Māori. The rate of ovarian cancer appears to be reducing over time (Te Aho o Te Kahu 2021a). The rate of ovarian cancer is somewhat higher for Māori (7 per 100,000 total population) compared with non-Māori (6 per 100,000 total population) (Robson et al 2010). The rate of ovarian cancer among Pacific peoples is also higher than that of the non-Māori, non-Pacific, non-Asian population (Meredith et al 2012). Relevant to the olaparib gap above, international studies have shown that about 10–20 percent of epithelial ovarian cancer patients are germline BRCA positive, with the highest prevalence in those with high-grade serous subtype (Alsop et al 2012; Zhang et al 2011). A small study in Aotearoa found that 16 percent of patients with high-grade serous cancer of the ovary, fallopian tube or peritoneum who were diagnosed between 2015 and 2016 and referred for genetic testing were germline BRCA positive (Fraser et al 2019).

Stage at diagnosis

Based on New Zealand Cancer Registry data, around 15 percent of ovarian cancers are diagnosed when the disease is localised (14 percent Māori, 13 percent New Zealand European), and 18 percent at a regional stage (15 percent Māori, 17 percent New Zealand European). Nearly two-thirds of ovarian cancers are diagnosed at an advanced stage (60 percent of total cases, 58 percent Māori, 63 percent New Zealand European). Only a small proportion of ovarian cancers remain unstaged on the registry (7 percent total, 12 percent Māori, 7 percent New Zealand European) (Gurney, Stanley, Jackson, et al 2020).

Survival

Around 40 percent of those diagnosed with ovarian cancer will survive to five years (43 percent Māori, 39 percent non-Māori (Gurney, Stanley, McLeod, et al 2020). Aotearoa is sixth out of seven high-income countries for five-year survival from ovarian cancer (Arnold et al 2019). There is currently a lack of robust stage-specific survival data for ovarian cancer in Aotearoa, although a study in one centre found that around 20 percent of patients with advanced disease survived to five years (Yeoh et al 2019). From 2007–2016 data, Māori patients with ovarian cancer are 62 percent more likely to die of their cancer than non-Māori patients with ovarian cancer (Gurney, Stanley, McLeod, et al 2020).

Mortality

On average over the last decade, there have been 194 deaths each year from ovarian cancer, including 15 Māori (Gurney, Robson, et al 2020; Te Aho o Te Kahu 2021a). Mortality rates for ovarian cancer are similar between Māori and non-Māori (both 3 per 100,000 total population) (Gurney, Robson, et al 2020). The ovarian cancer mortality rate is also similar between Pacific peoples and the non-Māori, non-Pacific, non-Asian population (both 2 per 100,000) (Te Aho o Te Kahu 2021a).

Head and neck cancer

Table 7.16: Nivolumab for head and neck cancer

Indication description	Head and neck squamous cell cancer (HNSCC), locally recurrent or metastatic, second-line therapy
Medicine option to fill the gap	Nivolumab
Description of medicine class	Immune checkpoint inhibitor (monoclonal antibody targeting PD-1 protein)
Intent of treatment	Non-curative
Pharmac status at time of analysis	No application received
ESMO-MCBS clinical benefit score and summary of data informing the score	5 Compared with chemotherapy Gain in median overall survival of 2.4 months, with durable response (two-year survival gain 10.9%) Progression-free survival did not contribute to the score. Quality-of-life results did not contribute to the score. Reduced toxicity contributed to the score. www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-189-1
Current clinical practice in Aotearoa and how this would change if the gap were filled	In Aotearoa, the current treatment for these patients is chemotherapy or best supportive care. If nivolumab were funded for this indication it would become an additional line of active treatment. It would be used alone, rather than being added to chemotherapy.
Pharmac estimate of eligible population size	A Pharmac estimate of the eligible population size was not readily available at time of publication. The population size was not able to be estimated by other means.
How this medicine would be given	This medicine is given by infusion. Nivolumab would be given every two or four weeks until disease progression (or unacceptable toxicity).
Patient and whānau considerations	This treatment would become an additional treatment option for these patients, with the potential clinical benefit described above. The current approach is either chemotherapy or best supportive care. This would mean that, compared with the current approach, there would generally be more treatment appointments to attend. Nivolumab would be administered in the outpatient infusion centre, so patients would need to travel, but there would be no prescription charge. There may be other medicines needed to manage side effects that may have a prescription charge. There are some particular side effects associated with immune checkpoint inhibitors that are quite different to the side effects of chemotherapy. These can develop long after treatment has stopped and may require specialised management. Treatment would continue until there is progression of the disease (or intolerable side effects).

Health system resource considerations	Additional treatment appointments may be required. Additional follow-up appointments required. Additional chair time for administration of treatment may be required. Increased demand for laboratory and pathology services to monitor for treatment toxicities. Increased demand for radiology services to assess for disease progression (subject to any funding criteria). Potential for increased demand for supportive care and toxicity management (including health care professionals' time and pharmaceuticals).

Epidemiology of head and neck cancer

Incidence

Head and neck cancers are among the top-10 most commonly diagnosed cancers in Aotearoa – with an average of 550 people diagnosed each year, including 55 Māori (Te Aho o Te Kahu 2021a). The rate of head and neck cancer is similar for Māori and non-Māori (both 6 per 100,000). The rate of head and neck cancer among Pacific peoples (8 per 100,000) appears to be higher than that of the non-Māori, non-Pacific, non-Asian population (6 per 100,000) (Te Aho o Te Kahu 2021a).

Stage at diagnosis

Based on New Zealand Cancer Registry data, the majority of head and neck cancers are diagnosed at either the local stage (24 percent of total cases, 14 percent Māori, 27 percent New Zealand European) or a regional stage, when the disease has spread around the region of origin (32 percent total, 35 percent Māori, 31 percent New Zealand European). While the registry records less than 10 percent of head and neck cancer patients as being diagnosed with advanced disease (7 percent total, 9 percent Māori, 6 percent New Zealand European), more than one-third of diagnoses remain unstaged on the registry (37 percent total, 42 percent Māori, 36 percent New Zealand European) (Gurney, Stanley, Jackson, et al 2020).

Survival

Around two-thirds of those diagnosed with head and neck cancer will survive to five years (64 percent Māori, 64 percent non-Māori) (Soeberg et al 2012). There is currently a lack of robust stage-specific survival data for head and neck cancer in Aotearoa. Based on estimates from 2001–2004, Māori head and neck cancer patients had 37 percent greater excess mortality than non-Māori patients (Soeberg et al 2012).

Mortality

On average over the last decade, there have been 170 deaths each year from head and neck cancer, including 17 Māori (Gurney, Robson, et al 2020; Te Aho o Te Kahu 2021a). Mortality rates for head and neck cancer are higher for Māori (2 per 100,000) compared with non-Māori (1 per 100,000). The head and neck cancer mortality rate is also higher for Pacific peoples (3 per 100,000) than for the non-Māori, non-Pacific, non-Asian population. (1 per 100,000) (Te Aho o Te Kahu 2021a).

Skin cancer

Table 7.17: Nivolumab or pembrolizumab for melanoma (adjuvant)

Indication description	Melanoma, stage III, adjuvant therapy after surgery (complete resection)		
Medicine option to fill the gap	Nivolumab OR Pembrolizumab		
Description of medicine class	Immune checkpoint inhibitor (monoclonal antibodies targeting PD-1 protein)		
Intent of treatment	Curative		
Pharmac status at time of analysis	Nivolumab: no application received Pembrolizumab: Application deferred pending further data. This means that Pharmac has not ranked the application, and it has received advice that additional data is expected. Note: At the time of publication, the Pharmac status had been updated to under assessment – this means that Pharmac has received clinical advice regarding this funding application, and it is working to compare this against other options for funding. https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P000008ptx2/p000298		
ESMO-MCBS clinical benefit score and summary of data informing the score	Nivolumab	A	Compared with ipilimumab: Overall survival did not contribute to the score Gain in median relapse-free survival at one year of 9.7% Quality-of-life results did not contribute to the score. Fewer severe adverse events were noted, but these did not contribute to the score. Note: These were the results in a comparison against ipilimumab, which is not funded in Aotearoa. The relevant comparator for Aotearoa would be no active treatment and 'watch and wait'. Clinical advice indicated that against this comparator the ESMO-MCBS score would likely be at least B. www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-174-1
	Pembrolizumab	A	Compared with placebo: Overall survival did not contribute to the score. Gain in median relapse-free survival at one year of 14.4%. Quality-of-life results did not contribute to the score. A higher rate of acute and persisting adverse effects was noted, but this did not contribute to the score. www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-173-1

Current clinical practice in Aotearoa and how this would change if the gap were filled	In Aotearoa, the current approach for these patients is to 'watch and wait' after surgery. This means that patients do not receive any adjuvant treatment and are followed closely to detect tumour recurrence. If nivolumab or pembrolizumab were funded for this indication, either would become an active consolidation treatment to enhance the efficacy of surgical removal of the cancer.
Pharmac estimate of eligible population size	Size of eligible population is difficult to estimate because of data limitations (CaTSoP 2020). A Pharmac estimate of the eligible population size was not readily available at time of publication. The population size was not able to be estimated by other means. For reference purposes only, about 4 percent of melanoma patients are diagnosed with melanoma that has spread to regional lymph nodes (an approximation for stage III disease). This would equate to 96 people [0.04*2400=96]. This does not include any estimate of surgical resectability, however. See '**Epidemiology of melanoma skin cancers**' section below.
How this medicine would be given	These medicines are given by infusion. Nivolumab would be given every two or four weeks for about one year or until disease progression (or unacceptable toxicity). Pembrolizumab would be given every three or six weeks for about one year or until disease progression (or unacceptable toxicity).
Patient and whānau considerations	This treatment would become an active adjuvant treatment option for these patients, with the potential clinical benefit described above. Compared with the current approach ('watch and wait'), there would generally be more treatment appointments to attend. These treatments would be administered in the outpatient infusion centre, so patients would need to travel, but there would be no prescription charge. There may be other medicines needed to manage side effects that may have a prescription charge. There would be more side effects expected when compared to the current approach of no active treatment. There are some particular side effects associated with immune checkpoint inhibitors that are quite different to the side effects of chemotherapy. These can develop long after treatment has stopped and may require specialised management. Treatment would continue for a maximum of one year, or until there is progression of the disease (or intolerable side effects).
Health system resource considerations	Additional treatment appointments required. Additional follow-up appointments required. Additional chair time for administration of treatment required. Increased demand for laboratory and pathology services to monitor for treatment toxicities. Increased demand for radiology services to assess for disease recurrence (subject to any funding criteria). Potential for increased demand for supportive care and toxicity management (including health care professionals' time and pharmaceuticals). Potential for reduced demand for immunotherapy in the stage IV setting (where the duration of treatment would generally be longer) may offset some of the resource requirements described above.

Table 7.18: Dabrafenib with trametinib for melanoma (adjuvant)

Indication description	Melanoma, stage III, BRAF+ve V600, adjuvant therapy after surgery (complete resection)
Medicine option to fill the gap	Dabrafenib with trametinib
Description of medicine class	Dabrafenib: targeted treatment (small molecule targeting BRAF protein) Trametinib: targeted treatment (small molecule targeting MEK protein)
Intent of treatment	Curative
Pharmac status at time of analysis	No application received
ESMO-MCBS clinical benefit score and summary of data informing the score	A Compared with placebo: Overall survival did not contribute to the score. Gain in median relapse-free survival of 27.9 months with durable response (three-year relapse-free survival gain 19%) Quality of life was reported as an exploratory outcome and did not contribute to the score. Toxicity results did not contribute to the score. www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-172-1
Current clinical practice in Aotearoa and how this would change if the gap were filled	In Aotearoa, the current approach for these patients is to 'watch and wait' after surgery. This means that patients do not receive any adjuvant treatment and are followed closely to detect tumour recurrence. If dabrafenib and trametinib were funded for this indication, they would become an active adjuvant treatment to enhance the efficacy of surgical removal of the cancer.
Pharmac estimate of eligible population size	A Pharmac estimate of the eligible population size was not readily available at time of publication. The population size was not able to be estimated by other means. For reference purposes only, about 4 percent of melanoma patients (96 people per year) are diagnosed with melanoma that has spread to regional lymph nodes (an approximation for stage III disease). Applying a BRAF+ve V600 proportion of 33% to that would equate to about 32 people per year. This does not include any estimate of surgical resectability, however. See Table 7.17 above and 'epidemiology of melanoma skin cancers' section below.
How this medicine would be given	These medicines are taken orally. Dabrafenib is a capsule that is generally taken twice daily – the standard dosing is two capsules taken for each dose. Trametinib is a tablet that is generally taken once a day – the standard dosing is one tablet for each dose. Treatment is continued for one year (or until disease recurrence or unacceptable toxicity).
Patient and whānau considerations	This treatment would become an active adjuvant treatment option for these patients, with the potential clinical benefit described above. Compared with the current approach ('watch and wait'), there would be tablets to take. These could be taken at home, but a prescription charge would be payable. There would be more follow-up appointments needed. There may be other medicines needed to manage side effects that may also have a prescription charge. There would be more side effects expected when compared to the current approach of no active treatment. Treatment would continue for one year, unless there was progression of the disease (or intolerable side effects).

Health system resource considerations	Additional follow-up appointments required. Increased demand for laboratory and pathology services to assess eligibility and monitor for treatment toxicities. Increased demand for radiology services to assess for disease progression (subject to any funding criteria). Potential for increased demand for supportive care and toxicity management (including health care professionals' time and pharmaceuticals).

Table 7.19: Nivolumab with ipilimumab for melanoma (unresectable)

Indication description	Melanoma, stage III or IV, unresectable, first line
Medicine option to fill the gap	Nivolumab with ipilimumab
Description of medicine class	Nivolumab: immune checkpoint inhibitor (monoclonal antibody targeting PD-1 protein) Ipilimumab: immune checkpoint inhibitor (monoclonal antibody targeting CTLA-4 protein)
Intent of treatment	Non-curative
Pharmac status at time of analysis	Application received February 2016 Ranked as an option for decline – this means this option would not be funded, even if budget allowed, unless new information came to light. https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P000008puXS/p001176
ESMO-MCBS clinical benefit score and summary of data informing the score	4 Compared with ipilimumab: Gain in median overall survival of 18.4 months, with durable response (five-year overall survival gain 26%) Gain in median progression-free survival of 8.6 months. No quality-of-life benefit. Higher toxicity and discontinuation rate. Note: These were the results in a comparison against ipilimumab, which is not funded in Aotearoa. The relevant comparator for Aotearoa would be nivolumab (or pembrolizumab) used in monotherapy. Clinical advice indicated that, against this comparator, the ESMO-MCBS score would likely be at least 4.
Current clinical practice in Aotearoa and how this would change if the gap were filled	In Aotearoa, the current treatment for these patients is nivolumab or pembrolizumab monotherapy. If nivolumab with ipilimumab were funded for this indication, ipilimumab would be added to nivolumab monotherapy for the first four treatment cycles, then nivolumab would continue as per current practice. Clinical advice indicated that ipilimumab would only be added in for particularly aggressive tumours.
Pharmac estimate of eligible population size	A Pharmac estimate of the eligible population size was not readily available at time of publication. The population size was not able to be estimated by other means. For reference purposes only, if we used the proportion of people diagnosed with melanoma that has spread to regional lymph nodes (4%) or at an advanced stage (5%) as to approximate stage III and IV melanoma, this would equate to 216 people [9%*2400=216]. This does not include any estimate of surgical resectability. See '**Epidemiology of melanoma skin cancers**' section below.
How this medicine would be given	These medicines are given by infusion. Ipilimumab and nivolumab would be given every three weeks for the first four cycles, and then nivolumab would continue to be given once every two or four weeks until disease progression (or unacceptable toxicity).

Patient and whānau considerations	This treatment would be added in at the start of treatment for high-risk patients, with the potential clinical benefit described above. The current approach is nivolumab or pembrolizumab in monotherapy. This would mean that, compared with the current approach, there would generally be a similar number of treatment appointments to attend, although the first four appointments would be longer. These treatments would be administered in the outpatient infusion centre, so there would be no prescription charge. There may be other medicines needed to manage side effects that may have a prescription charge. There are some particular side effects associated with immune checkpoint inhibitors that are quite different to the side effects of chemotherapy. These can develop long after treatment has stopped and may require specialised management. Treatment would continue until there is progression of the disease (or intolerable side effects).
Health system resource considerations	Additional chair time for administration of treatment required. Increased demand for laboratory and pathology services to monitor for treatment toxicities. Increased demand for radiology services to assess for disease progression (subject to any funding criteria). Potential for increased demand for supportive care and toxicity management (including health care professionals' time and pharmaceuticals).

Table 7.20: BRAF/MEK inhibitors for melanoma (unresectable)

Indication description	Melanoma, stage III or IV, BRAF +ve V600, unresectable, first-line therapy		
Medicine option to fill the gap	Dabrafenib with trametinib OR Encorafenib with binimetinib OR Vemurafenib with cobimetinib		
Description of medicine class	Dabrafenib, encorafenib, vemurafenib: targeted treatment (small molecules targeting BRAF protein) Trametinib, binimetinib, cobimetinib: targeted treatment (small molecules targeting MEK protein)		
Intent of treatment	Non-curative		
Pharmac status at time of analysis	No application received		
ESMO-MCBS clinical benefit score and summary of data informing the score	Dabrafenib with trametinib	5	Compared with vemurafenib: Gain in median overall survival of 8.0 months, with durable response (three-year overall survival gain 13%) Gain in median progression-free survival of 4.1 months. Quality of life was reported as an exploratory outcome and did not contribute to the score. A reduction in frequency of skin cancer side effects contributed to the score. Note: These were the results in a comparison against vemurafenib, which is not funded in Aotearoa. The relevant comparator for Aotearoa would be nivolumab or pembrolizumab. Clinical advice indicated that, against this comparator, the ESMO-MCBS score would likely be at least 4 for melanoma with a BRAF V600 mutation. www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-87-1

ESMO-MCBS clinical benefit score and summary of data informing the score (continued)	Encorafenib with binimetinib	4	Compared with vemurafenib: Gain in median overall survival of 16.7 months Gain in median progression-free survival of 7.6 months Quality-of-life and toxicity results did not contribute to this score. Note: These were the results in a comparison against vemurafenib, which is not funded in Aotearoa. The relevant comparator for Aotearoa would be nivolumab or pembrolizumab. Clinical advice indicated that, against this comparator, the ESMO-MCBS score would likely be at least 4 for melanoma with a BRAF V600 mutation. www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-238-1
	Vemurafenib with cobimetinib	4	Compared with vemurafenib: Gain in median overall survival of 4.9 months Gain in median progression-free survival of 5.1 months. Quality-of-life results did not contribute to the score. A reduction in frequency of skin cancer side effects contributed to the score. Note: These were the results in a comparison against vemurafenib, which is not funded in Aotearoa. The relevant comparator for Aotearoa would be nivolumab or pembrolizumab. Clinical advice indicated that, against this comparator, the ESMO-MCBS score would likely be at least 4 for melanoma with a BRAF V600 mutation. www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-88-1
Current clinical practice in Aotearoa and how this would change if the gap were filled	In Aotearoa, the current treatment for unresectable stage III or IV melanoma (including those that are BRAF +) is pembrolizumab or nivolumab. If one of these BRAF-MEK combination treatments were funded for this indication, this would become an alternative first-line treatment option for people with BRAF V600 +ve melanoma.		
Pharmac estimate of eligible population size	A Pharmac estimate of the eligible population size was not readily available at time of publication. The population size was not able to be estimated by other means. For reference purposes only, if we assumed 33% of the number of people estimated to be diagnosed with stage III and IV melanoma were BRAF V600+, that would equate to about 71 people per year [33%*216=71]. This does not include any estimate of surgical resectability, however. See Table 7.19 above and 'epidemiology of melanoma skin cancers' section below.		

How this medicine would be given	These medicines are taken orally. Treatment would require at least two separate tablets and/or capsules, generally taken up to twice daily. Treatment would continue until disease progression or unacceptable toxicity. In order to determine eligibility for this medicine, a particular test would need to be done using a sample of the tumour.
Patient and whānau considerations	This treatment would become an alternative treatment option for these patients, with the potential clinical benefit described above. In order to determine eligibility for this medicine, a particular laboratory test would need to be done using a sample of the tumour – this might mean an extra surgical procedure. The current approach is to treat with nivolumab or pembrolizumab. This would mean that, compared with the current approach, there would be tablets to take, but these could be taken at home rather than needing to travel to an infusion centre. A prescription charge would be payable. The side effects of these oral treatments are likely to be very different to the current treatment approach. Treatment would continue until there was progression of the disease (or intolerable side effects).
Health system resource considerations	Fewer treatment appointments required. Reduced chair time for administration of treatment. Increased demand for laboratory and pathology services to determine treatment eligibility and monitor for treatment toxicities. Increased demand for radiology services to assess for disease progression (subject to any funding criteria).

Epidemiology of melanoma skin cancers

Incidence

Melanoma skin cancers are the fourth most common cancers diagnosed in Aotearoa – with an average of 2,400 people diagnosed each year, including 46 Māori (Te Aho o Te Kahu 2021a). The rate of melanoma is substantially higher for non-Māori (primarily New Zealand Europeans) compared with Māori (5 per 100,000 for Māori, 29 per 100,000 for non-Māori) (Te Aho o Te Kahu 2021a). Similarly, the rate of melanoma among Pacific peoples is considerably lower than that of the non-Māori, non-Pacific, non-Asian population (Meredith et al 2012). Melanomas harbour BRAF mutations in 40–50 percent of cases (Greaves et al 2013; Wolfe et al 2021), although a small study in Aotearoa found a lower prevalence of 33 percent (Jones et al 2016).

Stage at diagnosis

Based on New Zealand Cancer Registry data, the vast majority of melanomas are diagnosed at a local stage (83 percent of total cases, 70 percent Māori, 82 percent New Zealand European). Around 8 percent are diagnosed at a regional stage (4 percent direct extension through the dermis, 4 percent spread to regional lymph nodes), and 5 percent when the cancer is at an advanced stage. Only 5 percent remain un-staged on the registry (Gurney, Stanley, Jackson, et al 2020).

Survival

More than 80 percent of those diagnosed with melanoma will survive to five years (80 percent Māori, 89 percent non-Māori) (Gurney, Stanley, McLeod, et al 2020). There is currently a lack of robust stage-specific survival data for melanoma in Aotearoa. From 2007–2016 data, Māori patients with melanoma are 2.5 times more likely to die from that cancer than non-Māori patients – however, this disparity must be considered alongside the relative rarity of Māori death from melanoma (see Mortality below) (Gurney, Stanley, McLeod, et al 2020).

Mortality

On average over the last decade, there have been 350 deaths each year from melanoma, including six Māori (Gurney, Robson, et al 2020; Te Aho o Te Kahu 2021a). Mortality rates for melanoma are higher for non-Māori (primarily New Zealand Europeans) than for Māori (less than 1 per 100,000 for Māori, 3 per 100,000 for non-Maori). Similarly, mortality is lower for Pacific peoples (1 per 100,000) than for the non-Māori, non-Pacific, non-Asian population (4 per 100,000) (Te Aho o Te Kahu 2021a).

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REFERENCES

Alsop K, Fereday S, Meldrum C, et al. 2012. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. *Journal of Clinical Oncology* 30(21): 2654–63. DOI: 10.1200/jco.2011.39.8545 (accessed 4 April 2022).

Araghi M, Arnold M, Rutherford MJ, et al. 2021. Colon and rectal cancer survival in seven high-income countries 2010–2014: Variation by age and stage at diagnosis (the ICBP SURVMARK-2 project) [Article]. *Gut* 70(1): 114–26. DOI: 10.1136/gutjnl-2020-320625 (accessed 4 April 2022).

Arnold M, Rutherford MJ, Bardot A, et al. 2019. Progress in cancer survival, mortality, and incidence in seven high-income countries 1995–2014 (ICBP SURVMARK-2): a population-based study. *Lancet Oncology* 20(11): 1,493–505. DOI: 10.1016/s1470-2045(19)30456-5 (accessed 4 April 2022).

Australian Government Department of Health. 2022. *Pharmaceutical Benefits Scheme (PBS)*. URL: www.pbs.gov.au/pbs/home (accessed 3 March 2022).

Australian Government Department of Health. nd. *The Pharmaceutical Benefits Scheme (PBS): Browse by Body System*. URL: www.pbs.gov.au/browse/body-system (accessed 3 March 2022).

Aye PS, McKeage MJ, Tin Tin S, et al. 2021. Population-based incidence rates and increased risk of EGFR mutated non-small cell lung cancer in Māori and Pacifica in New Zealand. *PloS one* 16(5): e0251357. DOI: 10.1371/journal.pone.0251357.

Babar Z-U-D, Gammie T, Seyfoddin A, et al. 2019. Patient access to medicines in two countries with similar health systems and differing medicines policies: Implications from a comprehensive literature review. *Research in Social and Administrative Pharmacy* 15(3): 231–43. DOI: 10.1016/j.sapharm.2018.04.006 (accessed 4 April 2022).

Babar Z-U-D, Vitry A. 2014. Differences in Australian and New Zealand medicines funding policies. *Australian Prescriber* 37(5): 150–1.

Bach PB. 2009. Limits on Medicare's ability to control rising spending on cancer drugs. *New England Journal of Medicine* 360(6): 626–33. DOI: 10.1056/NEJMhpr0807774 (accessed 4 April 2022).

Booth CM, Eisenhauer EA. 2012. Progression-free survival: Meaningful or simply measurable? *Journal of Clinical Oncology* 30(10): 1,030–33. DOI: 10.1200/JCO.2011.38.7571 (accessed 4 April 2022).

Breast Cancer Foundation New Zealand. 2022. *30,000 Voices: Informing a better future for breast cancer in Aotearoa New Zealand*. Auckland: Breast Cancer Foundation New Zealand.

Cancer Care Ontario. nd. *Drug Formulary*. URL: www.cancercareontario.ca/en/drugformulary/drugs (accessed 3 March 2022).

Cancer Institute NSW. nd, a. *eviQ: About us*. NSW Government. URL: www.eviq.org.au/pages/about-us (accessed 3 March 2022).

Cancer Institute NSW. nd, b. *eviQ: Search*. NSW Government. URL: www.eviq.org.au/search?searchtext=cyclophosphamide (accessed 3 March 2022).

Cancer Institute NSW. 2021a. *Basal Cell Carcinoma Locally Advanced or Metastatic soNIDEGib*. URL: www.eviq.org.au/medical-oncology/melanoma/non-melanoma/3410-basal-cell-carcinoma-locally-advanced-or-meta#evidence (accessed 22 March 2022).

Cancer Institute NSW. 2021b. *Basal Cell Carcinoma Locally Advanced or Metastatic vismodegib*. URL: www.eviq.org.au/medical-oncology/melanoma/non-melanoma/1918-basal-cell-carcinoma-locally-advanced-or-meta#evidence (accessed 22 March 2022).

CaTSoP. 2019. *Record of the Cancer Treatment Subcommittee of PTAC meeting held at PHARMAC on 5 April 2019.* Cancer Treatment Subcommittee of PTAC (CaTSoP). URL: https://pharmac.govt.nz/assets/ptac-cancer-treatment-subcommittee-record-2019-04.pdf (accessed 11 April 2022).

CaTSoP. 2020. *Record of the Cancer Treatment Subcommittee of PTAC meeting held on 15 and 16 October 2020.* Cancer Treatment Subcommittee of PTAC (CaTSoP). URL: https://pharmac.govt.nz/assets/2020-10-Cancer-Treatment-Subcommittee-Record-published-25-February-2021.pdf (accessed 11 April 2022).

CaTSoP. 2021. *Record of the Cancer Subcommittee of PTAC Meeting held on 9 July 2021.* Cancer Treatment Subcommittee of PTAC (CaTSoP). URL: https://pharmac.govt.nz/assets/2021-07-Catsop_record.pdf (accessed 11 April 2022).

Chamberlain J, Sarfati D, Cunningham R, et al. 2013. Incidence and management of hepatocellular carcinoma among Māori and non-Māori New Zealanders. *Australian & New Zealand Journal of Public Health* 37: 520–26.

Cheema PK, Gavura S, Migus M, et al. 2012. International variability in the reimbursement of cancer drugs by publically funded drug programs. *Current Oncology* 19(3): e165–76. DOI: 10.3747/co.19.946 (accessed 4 April 2022).

Cheng S, McDonald EJ, Cheung MC, et al. 2017. Do the American Society of Clinical Oncology Value Framework and the European Society of Medical Oncology Magnitude of Clinical Benefit Scale measure the same construct of clinical benefit? *Journal of Clinical Oncology* 35(24): 2,764–71. DOI: 10.1200/JCO.2016.71.6894 (accessed 4 April 2022).

Cherny NI, Dafni U, Bogaerts J, et al. 2017. ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28(10): 2,340–66. DOI: 10.1093/annonc/mdx310 (accessed 4 April 2022).

Cherny NI, Dafni U, Pentheroudakis G, et al. 2022. "The first ones now, will later be last": Understanding the importance of historical context when reading ESMO-MCBS scores. *ESMO Open* 7(2). DOI: 10.1016/j.esmoop.2022.100413 (accessed 4 April 2022).

Cherny NI, de Vries EGE, Dafni U, et al. 2018. Comparative assessment of clinical benefit using the ESMO-Magnitude of Clinical Benefit Scale Version 1.1 and the ASCO Value Framework Net Health Benefit Score. *Journal of Clinical Oncology* 37(4): 336–49. DOI: 10.1200/JCO.18.00729 (accessed 4 April 2022).

Cherny NI, Sullivan R, Dafni U, et al. 2015. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). *Annals of Oncology* 26(8): 1,547–73. DOI: 10.1093/annonc/mdv249 (accessed 4 April 2022).

Cohen R, Martinez M, Cha A, et al. 2021. *Health Insurance Coverage: Early release of estimates from the National Health Interview Survey, January–June 2021*. National Center for Health Statistics. URL: www.cdc.gov/nchs/data/nhis/earlyrelease/insur202108-508.pdf (accessed 24 February 2022).

Cunningham R, Sarfati D, Stanley J, et al. 2015. Cancer survival in the context of mental illness: a national cohort study. *General Hospital Psychiatry* 37(6): 501–06. DOI: 10.1016/j.genhosppsych.2015.06.003 (accessed 4 April 2022).

Dafni U, Karlis D, Pedeli X, et al. 2017. Detailed statistical assessment of the characteristics of the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) threshold rules. *ESMO Open* 2(4). DOI: 10.1136/esmoopen-2017-000216 (accessed 4 April 2022).

Davis LE, Bogner E, Coburn NG, et al. 2020. Stage at diagnosis and survival in patients with cancer and a pre-existing mental illness: a meta-analysis. *Journal of Epidemiology and Community Health* 74(1): 84. DOI: 10.1136/jech-2019-212311 (accessed 4 April 2022).

Dreicer JJ, Mailankody S, Fakhrejahani F, et al. 2017. Clinically meaningful benefit: real world use compared against the American and European guidelines. *Blood Cancer Journal* 7(12): 645. DOI: 10.1038/s41408-017-0009-8 (accessed 4 April 2022).

ESMO. nd, a. *ESMO-Magnitude of Clinical Benefit Scale Booklet*. European Society for Medical Oncology. Lugano: European Society for Medical Oncology (ESMO) Scientific Affairs. URL: www.esmo.org/content/download/288502/5736211/1/ESMO-MCBS-Booklet.pdf (accessed 4 April 2022).

ESMO. nd, b. *ESMO-Magnitude of Clinical Benefit Scale V1.1 Instructions*. URL: www.esmo.org/content/download/117394/2059186/1/ESMO-MCBS-Version-1-1-Instructions.pdf (accessed 4 April 2022).

ESMO. 2021. *Seven Steps to Take Assessment of Clinical Benefit of Anticancer Medicines to the Next Level*. URL: https://perspectives.esmo.org/news/seven-steps-to-take-assessment-of-clinical-benefit-of-anticancer-medicines-to-the-next-level (accessed 4 April 2022).

Evans J, Laking G, Strother M, et al. 2016. Mind the gap: An analysis of foregone health gains from unfunded cancer medicines in New Zealand. *Seminars in Oncology* 43(6): 625–37. DOI: 10.1053/j.seminoncol.2016.10.004 (accessed 4 April 2022).

Fearnley D, Kerse N, Nixon G. 2016. The price of 'free'. Quantifying the costs incurred by rural residents attending publically funded outpatient clinics in rural and base hospitals. *Journal of Primary Health Care* 8(3): 204–09. DOI: 10.1071/hc16014 (accessed 4 April 2022).

Fraser K, Tan AL, Innes C, et al. 2019. Patterns of referral and uptake of BReast CAncer (BRCA) gene testing of eligible women with ovarian cancer in New Zealand. *New Zealand Medical Journal* 132(1490): 26–35.

Fundytus A, Sengar M, Lombe D, et al. 2021. Access to cancer medicines deemed essential by oncologists in 82 countries: an international, cross-sectional survey. *The Lancet Oncology* 22(10): 1367–77. DOI: 10.1016/S1470-2045(21)00463-0 (accessed 4 April 2022).

Goodyear-Smith F, Ashton T. 2019. New Zealand health system: Universalism struggles with persisting inequities. *The Lancet* 394(10196): 432–42. DOI: 10.1016/S0140-6736(19)31238-3 (accessed 4 April 2022).

Gordon LG, Elliott TM, Olsen CM, et al. 2018. Out-of-pocket medical expenses for Queenslanders with a major cancer. *Medical Journal of Australia* 208(11): 497. DOI: 10.5694/mja17.00815 (accessed 4 April 2022).

Greaves WO, Verma S, Patel KP, et al. 2013. Frequency and spectrum of BRAF mutations in a retrospective, single-institution study of 1112 cases of melanoma. *The Journal of molecular diagnostics : JMD* 15(2): 220–6. DOI: 10.1016/j.jmoldx.2012.10.002.

Gurney J, Robson B, Koea J, et al. 2020. The most commonly diagnosed and most common causes of cancer death for Māori New Zealanders. *New Zealand Medical Journal* 133(1521): 77–96.

Gurney J, Stanley J, Jackson C, et al. 2020. Stage at diagnosis for Māori cancer patients: disparities, similarities and data limitations. *New Zealand Medical Journal* 133(1508): 43–64.

Gurney J, Stanley J, McLeod M, et al. 2020. Disparities in cancer-specific survival between Māori and non-Māori New Zealanders, 2007–2016. *JCO Global Oncology* (6): 766–74. DOI: 10.1200/go.20.00028 (accessed 4 April 2022).

Gyawali B, de Vries EGE, Dafni U, et al. 2021. Biases in study design, implementation, and data analysis that distort the appraisal of clinical benefit and ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) scoring. *ESMO Open* 6(3): 100117. DOI: 10.1016/j.esmoop.2021.100117 (accessed 4 April 2022).

Gyawali B, Eisenhauer E, Tregear M, et al. 2022. Progression-free survival: It is time for a new name. *The Lancet Oncology* 23(3): 328–30. DOI: 10.1016/S1470-2045(22)00015-8 (accessed 4 April 2022).

Haslam A, Hey SP, Gill J, et al. 2019. A systematic review of trial-level meta-analyses measuring the strength of association between surrogate end-points and overall survival in oncology. *European Journal of Cancer* 106: 196–211. DOI: 10.1016/j.ejca.2018.11.012 (accessed 4 April 2022).

Hill S, Sarfati D, Blakely T, et al. 2010. Ethnicity and management of colon cancer in New Zealand. *Cancer* 3: 205–14.

Hofmarcher T, Keel G, Lindgren P. 2021. *Health Spending on Cancer Drugs and Unmet Patient Needs in Asia-Pacific*. The Swedish Institute for Health Economics (IHE). URL: https://ihe.se/en/publicering/cancer-drug-spending-in-asia-pacific/ (accessed 4 April 2022).

Hwang TJ, Gyawali, B. 2019. Association between progression-free survival and patients' quality of life in cancer clinical trials. *International Journal of Cancer* 144(7): 1,746–51. DOI: 10.1002/ijc.31957 (accessed 4 April 2022).

Hynd A, Roughead EE, Preen DB, et al. 2008. The impact of co-payment increases on dispensings of government-subsidised medicines in Australia. *Pharmacoepidemiology and Drug Safety* 17(11): 1,091–99. DOI: 10.1002/pds.1670 (accessed 4 April 2022).

Jackson C, Sharples K, Firth M, et al. 2015. *The PIPER Project: An internal examination of colorectal cancer management in New Zealand. Final study report to the Health Research Council and Ministry of Health.* URL: www.fmhs.auckland.ac.nz/assets/fmhs/sms/ctnz/docs/THE%20PIPER%20PROJECT%20Final%20deliverable%20report%207%20August%202015%20(HRC%2011_764%20FINDLAY).pdf (accessed 4 April 2022).

Jatrana S, Crampton P, Norris P. 2011. Ethnic differences in access to prescription medication because of cost in New Zealand. *Journal of Epidemiology & Community Health* 65(5): 454–60. DOI: 10.1136/jech.2009.099101 (accessed 4 April 2022).

Jiang DM, Chan KKW, Jang RW, et al. 2019. Anticancer drugs approved by the Food and Drug Administration for gastrointestinal malignancies: Clinical benefit and price considerations. *Cancer Medicine* 8(4): 1,584–93. DOI: 10.1002/cam4.2058 (accessed 4 April 2022).

Jones AM, Ferguson P, Gardner J, et al. 2016. NRAS and EPHB6 mutation rates differ in metastatic melanomas of patients in the North Island versus South Island of New Zealand. *Oncotarget* 7(27): 41,017–30. DOI: https://doi.org/10.18632/oncotarget.9351.

Kantarjian H, Rajkumar SV. 2015. Why are cancer drugs so expensive in the United States, and what are the solutions? *Mayo Clinic Proceedings* 90(4): 500–4. DOI: 10.1016/j.mayocp.2015.01.014 (accessed 4 April 2022).

Kiesewetter B, Cherny NI, Boissel N, et al. 2020. EHA evaluation of the ESMO-Magnitude of Clinical Benefit Scale version 1.1 (ESMO-MCBS v1.1) for haematological malignancies. *ESMO Open* 5(1): e000611. DOI: https://doi.org/ 10.1136/esmoopen-2019-000611 (accessed 4 April 2022).

Lao C, Kuper-Hommel M, Laking G, et al. 2020. Evidence of inequitable use of chemotherapy in New Zealand colorectal cancer patients. *New Zealand Medical Journal* 133(1520): 15–26.

Lawrenson R, Lao C, Campbell I, et al. 2018. The use of trastuzumab in New Zealand women with breast cancer. *Asia-Pacific Journal of Clinical Oncology* 14(2): e152–60. DOI: https://doi.org/10.1111/ajco.12766 (accessed 4 April 2022).

Lichtenberg FR. 2021. The impact of pharmaceutical innovation on the longevity and hospitalization of New Zealand cancer patients, 1998–2017. *Expert Review of Pharmacoeconomics and Outcomes Research* 21(3): 476–77. DOI: https://doi.org/10.1080/14737167.2021.1871330 (accessed 4 April 2022).

McLeod M, Harris R, Purdie G, et al. 2010. Improving survival disparities in cervical cancer between Māori and non-Māori women in New Zealand: a national retrospective cohort study. *Australian and New Zealand Journal of Public Health* 34(2): 193–9. DOI: 10.1111/j.1753-6405.2010.00506.x (accessed 4 April 2022).

Medsafe. 2021. *New Zealand Data Sheet: IMFINZI® 50 mg/mL, concentrated solution for infusion*. Medsafe. URL: www.medsafe.govt.nz/profs/Datasheet/i/imfinziinf.pdf (accessed 4 April 2022).

Meredith I, Sarfati D, Ikeda T, et al. 2012. Cancer in Pacific people in New Zealand. *Cancer Causes Control* 23(7): 1,173–84. DOI: https://doi.org/10.1007/s10552-012-9986-x (accessed 4 April 2022).

Meyers DE, Meyers BS, Chisamore TM, et al. 2022. Trends in drug revenue among major pharmaceutical companies: A 2010–2019 cohort study. *Cancer* 128(2): 311–16. DOI: 10.1002/cncr.33934 (accessed 4 April 2022).

Ministry of Health. 2014. *Rangatiratanga*. URL: www.health.govt.nz/our-work/populations/maori-health/he-korowai-oranga/key-threads/rangatiratanga (accessed 15 March 2022).

Ministry of Health. 2019a. *Achieving Equity*. URL: www.health.govt.nz/about-ministry/what-we-do/work-programme-2019-20/achieving-equity (accessed 4 April 2022).

Ministry of Health. 2019b. *New Zealand Cancer Action Plan 2019–2029 – Te Mahere mō te Mate Pukupuku o Aotearoa 2019–2029*. Wellington: Ministry of Health.

Ministry of Health. 2020. *Longer, Healthier Lives: New Zealand's Health 1990–2017.* Wellington: Ministry of Health. URL: www.health.govt.nz/system/files/documents/publications/longer-healthier-lives-new-zealands-health-1990-2017.pdf (accessed 4 April 2022).

Ministry of Health. 2021. *Budget 2021: Vote Health.* URL: www.health.govt.nz/about-ministry/what-we-do/budget-2021-vote-healthwork-programme-2019-20/achieving-equity (accessed 4 April 2022).

Molto C, Hwang TJ, Borrell M, et al. 2020. Clinical benefit and cost of breakthrough cancer drugs approved by the US Food and Drug Administration. *Cancer* 126(19): 4,390–99. DOI: 10.1002/cncr.33095 (accessed 4 April 2022).

National Cancer Institute. 2020. *Clear Cell Renal Cell Carcinoma*. URL: https://www.cancer.gov/pediatric-adult-rare-tumor/rare-tumors/rare-kidney-tumors/clear-cell-renal-cell-carcinoma (accessed 12 April 2022).

Neugut AI, Prigerson HG. 2017. Curative, life-extending, and palliative chemotherapy: New outcomes need new names. *Oncologist* 22(8): 883–85. DOI: 10.1634/theoncologist.2017-0041 (accessed 4 April 2022).

New Zealand Government. 2021. *Prescription Subsidy Scheme*. URL: https://www.govt.nz/browse/health/gps-and-prescriptions/prescription-subsidy-scheme/ (accessed 4 April 2022).

New Zealand Parliamentary Counsel Office. nd. *New Zealand Public Health and Disability Act 2000: section 47: Objectives of Pharmac* URL: https://www.legislation.govt.nz/act/public/2000/0091/latest/DLM80878.html (accessed 4 April 2022).

Norris P, Tordoff J, McIntosh B, et al. 2016. Impact of prescription charges on people living in poverty: A qualitative study. *Research in Social and Administrative Pharmacy* 12(6): 893–902. DOI: 10.1016/j.sapharm.2015.11.001 (accessed 4 April 2022).

O'Donnell PH, Dolan ME. 2009. Cancer pharmacoethnicity: ethnic differences in susceptibility to the effects of chemotherapy. *Clinical Cancer Research : An Official Journal of the American Association for Cancer Research* 15(15): 4,806–14. DOI: https://doi.org/10.1158/1078-0432.Ccr-09-0344 (accessed 4 April 2022).

Pharmac. 2020a. *Cancer Medicine Funding: Parallel Assessment*. URL: https://pharmac.govt.nz/medicine-funding-and-supply/the-funding-process/from-application-to-funded-medicine-how-we-fund-a-medicine/cancer-medicine-funding-parallel-assessment/ (accessed 26 November 2021).

Pharmac. 2020b. *Factors for Consideration*. URL: https://pharmac.govt.nz/medicine-funding-and-supply/the-funding-process/policies-manuals-and-processes/factors-for-consideration/ (accessed 26 November 2021).

Pharmac. 2021a. *Pharmac Commits to Being More Transparent*. URL: https://pharmac.govt.nz/news-and-resources/news/2021-07-28-media-release-pharmac-commits-to-being-more-transparent (accessed 22 March 2022).

Pharmac. 2021b. *Priority Lists for Funding Applications*. URL: https://pharmac.govt.nz/medicine-funding-and-supply/the-funding-process/priority-lists/ (accessed 25 February 2022).

Pharmac. 2021c. *Proposal to Fund Treatments for Cancer and Asthma*. URL: https://pharmac.govt.nz/medicine-funding-and-supply/the-funding-process/priority-lists/ (accessed 11 April 2022).

Pharmac. 2022a. *Combined Pharmaceutical Budget*. URL: https://pharmac.govt.nz/medicine-funding-and-supply/the-funding-process/setting-and-managing-the-combined-pharmaceutical-budget-cpb/ (accessed 23 March 2022).

Pharmac. 2022b. *Decision to Fund Treatments for Cancer and Asthma*. URL: https://pharmac.govt.nz/news-and-resources/consultations-and-decisions/2022-03-16-decision-to-fund-treatments-for-cancer-and-asthma/ (accessed 23 March 2022).

Pharmac. 2022c. *How Pharmac Works*. URL: https://pharmac.govt.nz/about/what-we-do/how-pharmac-works/ (accessed 22 March 2022).

Prasad V. 2017. Do cancer drugs improve survival or quality of life? *BMJ* 359: j4528. DOI: 10.1136/bmj.j4528 (accessed 4 April 2022).

Robson B, Purdie G, Cormack D. 2010. *Unequal Impact II: Māori and Non-Māori Cancer Statistics by Deprivation and Rural-Urban Status, 2002–2006*. Wellington: Ministry of Health. URL: https://www.health.govt.nz/system/files/documents/publications/unequal-impact-ii.pdf (accessed 4 April 2022).

Rodwin MA. 2021. How the United Kingdom controls pharmaceutical prices and spending: Learning from its experience. *International Journal of Health Services* 51(2): 229–37. DOI: 10.1177/0020731421997094 (accessed 4 April 2022).

Savage P, Mahmoud S, Patel Y, et al. 2017. Cancer drugs: An international comparison of postlicensing price inflation. *Journal of Oncology Practice* 13(6): e538–42. DOI: 10.1200/JOP.2016.014431 (accessed 4 April 2022).

Schrag D. 2004. The price tag on progress — Chemotherapy for colorectal cancer. *New England Journal of Medicine* 351(4): 317–19. DOI: https://doi.org/10.1056/NEJMp048143 (accessed 4 April 2022).

Seneviratne S, Campbell I, Scott N, et al. 2014. Ethnic differences in timely adjuvant chemotherapy and radiation therapy for breast cancer in New Zealand: a cohort study. *BMC Cancer* 14(1): 839. DOI: 10.1186/1471-2407-14-839 (accessed 4 April 2022).

Soeberg M, Blakely T, Sarfati D, et al. 2012. *Cancer Trends: Trends in cancer survival by ethnic and socioeconomic group, New Zealand 1991–2004.* Wellington: University of Otago and Ministry of Health. URL: www.health.govt.nz/system/files/documents/publications/cancer-trends-survival-ethnic-socioeconomic-1991-2004_1.pdf (accessed 4 April 2022).

Soria JC, Mauguen A, Reck M, et al. 2013. Systematic review and meta-analysis of randomised, phase II/III trials adding bevacizumab to platinum-based chemotherapy as first-line treatment in patients with advanced non-small-cell lung cancer. *Ann Oncol* 24(1): 20–30. https://doi.org/10.1093/annonc/mds590.

Stevens W, Stevens G, Kolbe J, et al. 2007. Lung cancer in New Zealand: Patterns of secondary care and implications for survival. *Journal of Thoracic Oncology* 2(6): 481–93. DOI: 10.1097/JTO.0b013e31805fea3a (accessed 4 April 2022).

Tabernero J, Vyas M, Giuliani R, et al. 2016. Biosimilars: A position paper of the European Society for Medical Oncology, with particular reference to oncology prescribers. *ESMO Open* 1(6): e000142. DOI: 10.1136/esmoopen-2016-000142 (accessed 4 April 2022).

Te Aho o Te Kahu. 2021a. *He Pūrongo Mate Pukupuku o Aotearoa 2020, The State of Cancer in New Zealand 2020.* Wellington: Te Aho o Te Kahu. URL: https://teaho.govt.nz/static/reports/state-of-cancer-in-new-zealand-2020%20(revised%20March%202021).pdf (accessed 4 April 2022).

Te Aho o Te Kahu. 2021b. *Lung Cancer Quality Performance Indicator Action Plan*. Wellington: Te Aho o Te Kahu. URL: https://hcmsitesstorage.blob.core.windows.net/cca/assets/Lung_QPI_Action_Plan_FINAL_94ee771158.pdf (accessed 4 April 2022).

Tin Tin S, Elwood JM, Brown C, et al. 2018. Ethnic disparities in breast cancer survival in New Zealand: which factors contribute? *BMC Cancer* 18(1): 58. DOI: 10.1186/s12885-017-3797-0 (accessed 4 April 2022).

Vivot A, Jacot J, Zeitoun JD, et al. 2017. Clinical benefit, price and approval characteristics of FDA-approved new drugs for treating advanced solid cancer, 2000–2013; 2015. *Annals of Oncology* 28(5): 1,111–16. DOI: 10.1093/annonc/mdx053 (accessed 4 April 2022).

Vokinger KN, Hwang TJ, Grischott T, et al. 2020. Prices and clinical benefit of cancer drugs in the USA and Europe: a cost-benefit analysis. *Lancet Oncology* 21(5): 664–70. DOI: 10.1016/s1470-2045(20)30139-x (accessed 4 April 2022).

von Minckwitz G, Huang C-S, Mano MS, et al. 2018. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *New England Journal of Medicine* 380(7): 617–28. DOI: https://doi.org/10.1056/NEJMoa1814017 (accessed 4 April 2022).

Waitangi Tribunal. 2019. *Hauora: Report on Stage One of the Health Services and Outcomes Kaupapa Inquiry (WAI 2575)*. Wellington: Ministry of Justice. URL: https://forms.justice.govt.nz/search/Documents/WT/wt_DOC_152801817/Hauora%20W.pdf (accessed 4 April 2022).

Walsh M, Grey C. 2019. The contribution of avoidable mortality to the life expectancy gap in Māori and Pacific populations in New Zealand-a decomposition analysis. *New Zealand Medical Journal* 132(1,492): 46–60.

Wang S, Yang Q, Deng L, et al. 2021. An overview of cancer drugs approved through expedited approval programs and orphan medicine designation globally between 2011 and 2020. *Drug Discovery Today*. DOI: 10.1016/j.drudis.2021.12.021 (accessed 4 April 2022).

WHO. 2018. *Pricing of Cancer Medicines and Its Impacts*. Geneva: World Health Organization (WHO). URL: https://apps.who.int/iris/bitstream/handle/10665/277190/9789241515115-eng.pdf?ua=1 (accessed 4 April 2022).

WHO. 2019a. *Executive Summary. The Selection and Use of Essential Medicines 2019. Report of the 22nd WHO Expert Committee on the Selection and Use of Essential Medicines, 1–5 April 2019.* Geneva: World Health Organization (WHO).

WHO. 2019b. *The Selection and Use of Essential Medicines: Report of the WHO Expert Committee on Selection and Use of Essential Medicines, 2019 (including the 21st WHO model list of essential medicines and the 7th WHO model list of essential medicines for children)*. Geneva: World Health Organization (WHO). URL: https://apps.who.int/iris/handle/10665/330668 (accessed 4 April 2022).

WHO. 2020. *Selection of Essential Medicines at country Level: Using the WHO Model List of Essential Medicines to update a national essential medicines list*. Geneva: World Health Organization (WHO).

Wolfe AR, Chablani P, Siedow MR, et al. 2021. BRAF mutation correlates with worse local–regional control following radiation therapy in patients with stage III melanoma. *Radiation Oncology* 16(1): 181. https://doi.org/10.1186/s13014-021-01903-5.

Wonder M, Fisher R. 2016. Subsidised access to new melanoma drugs: in need of further innovation? *New Zealand Medical Journal* 129(1,440): 37–54.

Wonder M, Milne R. 2011. Access to new medicines in New Zealand compared to Australia. *New Zealand Medical Journal* 124(1,346): 12–28.

Yeoh S, Simcock B, Innes C, et al. 2019. Trends in the overall survival rates in women with advanced ovarian cancer in a single tertiary centre in New Zealand. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 59(6): 861–66. DOI: 10.1111/ajo.13076 (accessed 4 April 2022).

Zhang S, Royer R, Li S, et al. 2011. Frequencies of BRCA1 and BRCA2 mutations among 1,342 unselected patients with invasive ovarian cancer. *Gynecologic Oncology* 121(2): 353–7. DOI: 10.1016/j.ygyno.2011.01.020.